Introduction: Merkel cell carcinoma (MCC) is a rare and aggressive cutaneous neuroendocrine tumor. Prognostic factors currently included in the reference AJCC classification are mainly clinical. Aim(s): Our objectives were to analyse clinicopathological prognostic factors and molecules of 3 main signaling pathways (mTOR, CXCR4 and PD1/PDL1) potentially involved in MCCs. Activity of PD1/PD-L1 inhibitors has been recently shown. Materials and methods: In a multicenter retrospective study, we collected 136 tumor samples included in paraffin from 122 patients between 2005 and 2013. We analyzed histological characteristics on H&E-whole slides, and immunohistochemical characteristics on Tissue Microarrays. We collected clinical data and follow-up for 77 patients. Results: We observed that PD-L1, pmTOR and CXCR4 were expressed in tumour cells in 57%, 51% and 68% of MCC, and associated with the absence of MCPV (Merkel cell polyomavirus) (pmTOR, p=0.022), presence of necrosis (CXCR4, p=0.041) and metastasis (pmTOR p=0.015 and CXCR4 p=0.048). In multivariate analysis, younger age (p=0.017), female gender (p=0.04), presence of MCPV (p=0.009), presence of Tumor Infiltrating Lymphocytes (p=0.0013) and expression of PD-L1 by tumor cells (p=0.026) were associated with an improved overall survival. Conclusion: These results suggest the interest to combine MCPV status and immune score to help staging of MCCs, and point out that new therapies targeting mTOR and CXCR4 could be considered in those tumours. Keywords: merkel cell carcinoma, mtor, cxc4, pd-l1
**A2 - SELECTED FOR ORAL PRESENTATION**

Implication of Neuropilin-2 in the Progression of Small Intestinal Neuroendocrine Tumors: Towards a Promising Therapeutic Target?


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**Introduction:** Small intestinal neuroendocrine tumors (siNETs) are rare tumors that raise several clinical and therapeutic challenges. Current treatments are not efficient, in part because of a poor understanding of their mechanisms of progression. We recently highlighted some axon guidance molecules (AGMs) that might be implicated in the progression of siNETs. Among them, we are currently focusing our efforts on the semaphorin 3F receptor neuropilin-2 (NRP2). **Aim(s):** The aim is to validate NRP2 as a therapeutic target. **Materials and methods:** A tissue microarray gathering 34 cases of siNETs has been utilized to assess NRP2 expression. NRP2 serum level has been dosed in patients. In vitro, NRP2 expression has been silenced in the STC-1 cell line. An in vivo mouse model of tumor cell dissemination has also been used. **Results:** We demonstrate that NRP2 is highly expressed in human siNETs. In addition, NRP2 serum level is increased in patients compared to controls. While NRP2 silencing does not seem to impact cell viability, proliferation or apoptosis, the use of a NRP2 blocking antibody decreases the viability of wild-type STC-1 cells. These clones also show a decrease in VEGFR2 expression. When grafted in nude mice, NRP2 silencing induces a strong antitumoral effect, associated with a diminution of cell proliferation and a decreased mTOR activation. **Conclusion:** Our results suggest NRP2 as a potential promising therapeutic target for siNETs. Ongoing mechanistic studies aim at deciphering the underlying molecular mechanisms. **Keywords:** sinets, progression, nrp2
Angiogenic Circulating Biomarkers in Patients with Advanced Pancreatic Neuroendocrine Tumors Treated with Everolimus

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Introduction: More than 10% of patient treated with Everolimus develop early onset of resistance. The lacking of adequate predictive factors in the targeted hera makes challenging the early identification of non-responders patients. Aim(s): This is a biological prospective trial (clinicaltrials.gov:NCT02305810) in 38 patients treated with RAD001 which aims to find soluble predictive factors. Materials and methods: Blood tests to test circulating endothelial cells (CECs), circulating endothelial progenitor cells (CEPS), as well as soluble angiogenic factors - VEGF, bFGF and thrombospondin-1 (TSP-1) - have been collected at the baseline, after 1 and 3 months of treatment and at the progression. Results: Serum VEGF, bFGF and TSP-1 did not show any changing in levels from baseline to progression. CECs CD146+ tend to decrease in the first 3 months and raise at progression (p = 0.01). Apoptotic CECs are also significantly reduced after the first 3 moths of treatment (p<0.01) and the levels tend to remain low also at the time of progression (p=0.024). CEPs, identified by the following phenotype Syto16+CD45dimCD133+CD34+, did not show any significant correlation with treatment. Conclusion: CECs CD146 and apoptotic CECs tend to correlate to early response (at 3 months) but also with progression. These results could probably be related to the antiangiogenic effect of RAD001, which we would speculate to be maintained also beyond progression. The other soluble angiogenic factors did not show any predictive value. Keywords: pancreatic nets, biomarker, everolimus
Introduction: Sst5TMD4, which is derived from a non-canonical splicing process of sst5 receptor, is overexpressed in several endocrine tumors and associated with a worse prognosis. **Aim(s):** To assess the expression of sst5TMD4 in GEP-NETs, and evaluate its association with different pathways involved in GEP-NETs tumorigenesis. **Materials and methods:** Fresh-frozen tumour samples were collected from 40 patients and analysed for expression of mRNA transcripts by quantitative real-time-PCR included somatostatin receptors and sst5TMD4, death-domain associated protein(DAXX), transcriptional regulator ATP-dependent helicase(ATRX), multiple endocrine neoplasia(MEN1), Notch and angiogenic factors (VEGFR, angiopoietin(Ang)1, Ang2, Tie2, hypoxia inducible factors and thrombospondin (THBS). Tumor characteristics: pNETs/GI-NETs: 50%/50%; G1-G2: 40%-60%; TNM stage: I(17%), II(3%), III(20%), IV(47%); 20% were functioning tumors. **Results:** The expression of sst5TMD4 was higher in GI-NETs than in pNETs (median 53.8 vs 17.5 copy numbers, p<0.02). A higher sst5TMD4 expression was associated with more advanced disease (median 38.17 vs 18.22 cn in patients with stage IV vs stage I, p< 0.05). Sst5TMD4 expression significantly correlated with MEN1 (r=0.56), DAXX (r = 0.65) and Notch (r=0.62). **Conclusion:** sst5TMD4 expression differs by primary tumor site and tumor stage, suggesting a potential role in NET tumor biology. A positive correlation was found with pathways involved in NET tumorigenesis. Industry sponsored. **Keywords:** somatostatin receptor, neuroendocrine tumors
Introduction: Bronchial carcinoids (BC), typical (TC) or atypical (AC), are rare neoplasms arising from neuroendocrine cells spread in the respiratory epithelium. Microarray data analysis obtained comparing a pool of TC with a pool of AC samples showed TSC22D1 down-regulation in AC samples. The role of TSC22D1 in neuroendocrine tumors is unknown. Aim(s): To evaluate TSC22D1 protein levels in BC tissues and the association between its expression with clinical and pathological characteristics of the patients.

Materials and methods: TSC22D1 protein levels were evaluated in BC tissues derived from 20 patients. Molecular, clinical and pathological characteristics of the patients were collected. TSC22D1 expression was correlated with sex, age, Ki-67, tumor grade, nodal stage and progression-free survival (PFS).

Results: TSC22D1 expression was found in 50% of BC tissues. No association between TSC22D1 protein levels and age, sex and ki-67 was found. On the other hand, a significant association was found between TSC22D1 expression levels and tumor grade and nodal stage. The patients with BCs positive for TSC22D1 were characterised by a higher tumor grade, nodal stage and shorter PFS as compared to those patients with BCs negative for this protein.

Conclusion: TSC22D1 expression seems to associate with a more aggressive behaviour in BC.

Keywords: tsc22d1, bronchial carcinoids, aggressiveness
Introduction: Transcriptom analysis revealed that mRNA signatures of distinct metastatic phenotypes in pancreatic NETs (pNETs) exhibit differences in components of the Slit-Robo pathway. **Aim(s):** Delineating the role of Slit2 and its receptor Robo1 for pNET progression. **Materials and methods:** Expression analysis in human pNETs was determined by IHC and qPCR. Migration, colony formation, and metastasis of mouse orthotopic pNETs were evaluated using pNET cells with restored Slit2 expression or Robo1 inactivation. **Results:** IHC localized Robo1 receptor to tumor epithelia, thus capable to respond to secreted Slit2. Reduction of Robo1 mRNA tissue levels correlated to shorter time-to-progression in pNET patients. Functionally, restored Slit2 expression in Slit2-deficient BON cells inhibited proliferation, migration and colony formation. Conversely, Robo1 knockdown or sequestration of Slit2 had opposite effects in QGP cells. In vivo, mice harbouring Slit2-expressing BON tumors exhibited lower incidence of metastases. Mechanistically, Slit2 re-expression in BON cells enhanced, whereas loss of Robo1 in QGP cells reduced Ras activity. Consequently, Slit2 delayed cell cycle in BON cells, consistent with a growth suppressive function of Ras in endocrine cells. **Conclusion:** Our data assign to Slit2-Robo1 a novel function as metastasis suppressor and identified Ras as downstream mediator, which links Slit2-Robo1 to growth inhibition in pNETs. Loss of Slit2-Robo1 may contribute to metastatic progression in pNETs. **Keywords:** net, ras, slit, robo, metastasis, orthotopic
The Expression of IGF Signaling Pathway Genes Is Frequently Elevated in Pancreatic Neuroendocrine Tumors, but Is Downregulated in Metastases

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Introduction: Studies have implicated EGFR, IGF and mTOR signaling pathways in the regulation of pNET growth. Interpretation of these studies is complex due to tumor subtype heterogeneity and differences in molecular analysis. Aim(s): To examine gene and protein expression of EGFR, IGF and mTOR signaling pathway components in (non)insulinoma pNETs. Materials and methods: Insulinomas were analysed by qRT-PCR (n=48) and immunohistochemistry (n=88). Protein expression was compared with that of 92 non-insulinomas (12 gastrinomas, 11 glucagonomas, 10 vipomas and 59 non-functioning). Findings were compared with normal pancreatic islands and correlated with histopathological data and outcome. Results: Insulinomas showed low EGFR and high IGF2 expression. IGFBP2, IGFBP3 and IGFBP6 mRNA levels were 2-4 fold higher than in islets. High protein expression of IGF2, IGF1R and INSR (51-92% tumors) and low-moderate expression of p-S6k and p-4EBP1 (7-28%) was observed. Correlations were found between 1) ERK1 mRNA expression and that of numerous IGF pathway genes, 2) pERK and IGF1R protein expression, and 3) decrease of IGF pathway components and both metastatic disease and shorter 10-years disease-free survival. Non-insulinoma pNETs showed similar protein expression profiles as insulinomas. Conclusion: Our observations suggest that high expression of IGF signaling pathway components is a hallmark of pNETs, but not necessarily leads to increased mTOR signaling. Reduced expression of IGF pathway components may be an adverse prognostic factor in insulinomas. Keywords:
The Role of MAPK Signalling in Pancreatic Neuroendocrine Cancer

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Introduction: Upon diagnosis, 65% of pNET patients suffer from metastatic or locally unresectable disease. The receptor tyrosine kinase inhibitor sunitinib and the mTOR inhibitor everolimus have set precedence for successful targeted therapies in pNET disease. However, response prediction and treatment alternatives still do not meet medical needs. Recent studies revealed mutations in RAS oncogenes in a fraction of tumours, emphasising a potential role of the MAPK pathway as therapeutic target.

Aim(s): To study the consequences of pharmacologic inactivation of MEK or ERK kinases in pNET cells.

Materials and methods: BON-1 and QGP-1 cell lines are treated with either MEK or ERK inhibitors. Live cell analysis is performed to determine efficacy and growth inhibition. Induction of apoptosis is shown by cleaved caspase-3 and cell cycle regulation is analysed by flow cytometry. Changes in the MAPK and mTOR signalling network are determined by western blots and multiplex immunoassays.

Results: Both MEK and ERK inhibition show dose-dependent, anti-proliferative effects in both cell lines. MEK and ERK inhibition leads to cell cycle arrest and induction of apoptosis in BON-1. In contrast, in QGP-1 cleaved caspase-3 is only detected upon ERK inhibition.

Conclusion: Inhibition of MEK or ERK affects growth and cell cycle of BON-1 and QGP-1. Whether this effect is clinically relevant for treatment of pNETs needs to be tested in preclinical studies.

Keywords: pancreatic neuroendocrine tumors, mapk pathway
Potential Therapeutic Targets for Gastric Poorly Differentiated Neuroendocrine Carcinoma

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Introduction: Gastric poorly differentiated neuroendocrine carcinoma (G-PDNEC) is rare and aggressive. Patients often present with distant metastases at initial diagnosis. Aim(s): To investigate the expression of SSTR2A and some key components of the AKT/mTOR signaling pathway in G-PDNEC for potential target therapy. Materials and methods: We evaluated 127 G-PDNECs by immunohistochemistry. SSTR2A membranous positivity was graded from 0-3+. TSC2, P70S6K, and p4EBP1 cytoplasmic staining, p-mTOR nuclear staining, and pAKT, PTEN nuclear/cytoplasmic staining were scored as positive if >5% of cells stained. Results: The G-PDNECs arose from the gastric upper (n=28), middle (n=32), and lower (n=67) parts. 90 patients (71%) presented with stage III, and 36 (28%) with stage IV. 28 (22%) died of disease (median 18 months), with 11 (9%) dead within a year; 33 (26%) were alive with disease (median follow-up 16 months). 58 (46%) of tumors showed some degree of SSTR2A positivity, but only 9 (7%) showed strong (3+) positivity. P70S6K strong positivity was seen in 19% (24), p4EBP1 positivity in 42%, and p-mTOR nuclear positivity in 61% of tumors. Of note, p-mTOR staining was usually most strongly positive along the leading/infiltrative edge of the tumor. Conclusion: We suggest an important role for mTOR pathway activation in G-PDNEC tumor infiltration. Given the poor disease prognosis with standard chemotherapeutic regimens, investigation of targeted therapy may be promising. Keywords: gastric, neuroendocrine carcinoma, mtor pathway, sstr, targeted therapies
Introduction: SSA represents the standard of care for controlling symptoms of patients with functional GEP-NEN and have anti-proliferative effects. Molecular targeted therapies (MTT) against angiogenesis resulted in an increased PFS, however, due to primary and acquired resistance to MTT, the impact on OS remains unclear. One of the most pivotal questions, whether combining SSA with novel MTT will result in enhanced anti-proliferative activity compared to monotherapy treatment, are lacking. Aim(s): The aim of this study is to characterize the interaction, optimal sequence and dose of SSA-based therapies (lanreotide) and MTT in PNEN. Materials and methods: SSTR1-5 were evaluated in BON-1, QGP-1 and Ins1 NEN cells via immunoblot and qRT-PCR. The impact of lanreotide on intracellular signaling, hormone secretion and cell proliferation was measured in cell lysates and supernatants. Results: SSTR were differently expressed in the cell lines. Lanreotide slightly influenced proliferation mainly via targeting pAKT and pERK, which was paralleled by decreased CgA expression and secretion. MTT positively influenced the expression of some SSTR. Cell viability was significantly reduced by regorafenib, sunitinib and everolimus. Synergistic effects of combined treatment were modest and time and dose dependent. Conclusion: SSTR are expressed in various NEN cell lines and influenced via MTT. The sequential combination of lanreotide and MTT on cell-viability has to be characterized in further in-vitro and in-vivo settings. Keywords: ssa, targeted therapies, sstr
Evaluation of Somatostatin and Dopamine Receptor Subtype 2 Expression in Pancreatic Neuroendocrine Neoplasms

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Introduction: Although somatostatin receptor subtype 2 (SSTR2) and dopamine type 2 receptor (D2R) are reported to be expressed in neuroendocrine neoplasms (NEN), there is a lack of data from studies on a large number of patients with pancreatic NEN. Aim(s): To evaluate the expression of SSTR2 and D2R in pancreatic NEN. Materials and methods: A total of 109 pancreatic NEN cases (median age 55 years, 44% male, 73% non-functioning tumors, 74% NET G1) that had undergone curative resection in our hospital were studied. Expression of SSTR2 and D2R was evaluated immunohistochemically using resected specimens. Several clinicopathological factors that affect the expression rate of SSTR2 and D2R were analyzed. Results: The expression rates of SSTR2 and D2R were 81% and 71%, respectively. Among 77 patients who expressed D2R, 81% (n=62) co-expressed SSTR2. Although SSTR2 seemed to be highly expressed in non-functioning tumors (85% vs. 69%, p=0.096) and in ENETS stage I/II (84% vs. 65%, p=0.062), no significant differences were observed in the expression rate of SSTR2 and D2R in association with other clinicopathological factors such as gender, WHO classification (G1 vs. G2/NEC), tumor location, and tumor size. In addition, the expression of SSTR2 and D2R did not affect progression-free survival or overall survival. Conclusion: D2R is highly expressed in pancreatic NEN and is frequently co-expressed with SSTR2. Dual inhibition of SSTR2 and D2R might thus be a novel therapeutic strategy for pancreatic NEN. Keywords: somatostatin receptor, dopamine receptor, sstr2, d2r
Antiproliferative Effects of Lanreotide in Neuroendocrine Tumors

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Introduction: Neuroendocrine tumors of the lung (BP-NETs, typical (AC) and atypical Carcinoids (ATC)) are rare tumors with heterogeneous behavior and molecular characteristics. For the intermediate proliferating BP-NETs treatment options are limited and unsatisfactory. Somatostatin analogues have not only anti-secretory effects, but also display antiproliferative features, as shown by PROMID and CLARINET trial. Nevertheless, their value in BP-NET is undefined so far. Aim(s): To establish a preclinical model for analysis of the antiproliferative effects of the somatostatin analogue Lanreotide on BP-NETs.

Materials and methods: NCI727, NCI-720 and the well differentiated new pancreatic NT3 cell line were characterized by immunocytochemistry and FACS for the expression of somatostatin receptors (sstR). Proliferation assays were performed with an optimized treatment protocol with Lanreotide as well as combinatory treatment with the PI3Kalpha inhibitor BYL719. Functional assays and multiplexed gene expression analysis (Nanostring technologies) will be shown on the meeting.

Results: With our optimized protocol Lanreotide inhibits effectively growth in TC- and ATC-cell lines. Its effect alone is moderate, but in combination with BYL719 we observed a better effect as good as in sstr-expressing NT3 cell line with Lanreotide alone. Conclusion: Lanreotide treatment is promising in BP-NETs and may be enhanced by combination with other targeted therapies.

Keywords: bronchopulmonary neuroendocrine tumors (bp-net), somatostatin analogues, lanreotide, signaling
Introduction: Gastro-entero-pancreatic neuroendocrine tumors (GEP-NETs) and metabolic syndrome (MS) are both increasing exponentially. MS has been associated with several non NET cancers. Aim(s): To evaluate the influence of MS and their individual criteria in GEP-NETs expression of cell proliferation and inflammation molecular markers. Materials and methods: IHC studies for Ki-67, FOXM1, IGF1R and IL-6 were performed in GEP-NETs paraffin-embedded tissue (n=39) and its expression was quantified by computerized image analysis. Results: MS nor individual parameters influenced Ki-67, FOXM1 or IGF1R expression in GEP-NETs, with the sole exception for peri-tumoral IL-6 expression, which was lower in pancreatic(PNETs) of patients with central obesity(p<0.05) and higher in gastro-intestinal (GI) NETs of patients with low HDL(p<0.05). FOXM1 and Ki-67, as well as, FOXM1 and IGF1R were found to be positively correlated (r²=0.673, p<0.01; r²=0.624, p<0.01, respectively). Conclusion: MS nor their individual parameters influenced any of the studied markers in GEP-NETs, except for low HDL that is associated with higher peri-tumoral inflammation in GI-NET. The positive correlation between FOXM1 and Ki-67 and IGF1R, confirms involvement of mTor and MAPK molecular pathways in GEP-NETs proliferation, thus their inhibition should be an important treatment target.


Keywords: gep-nets, metabolic syndrome, foxm1, igf1r, il-6, ki67
A Kinomic Approach to Identify Signaling Proteins Involved in Drug Resistance in GastroEnteroPancreatic Neuroendocrine Tumors

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Introduction: Most of the current therapeutic strategies used for neuroendocrine tumors (NETs) result in tumour growth stabilization, eventually followed by tumour progression. Thus, despite their original characteristics, NETs exhibit similar resistance features to treatments than other more common tumours. Aim(s): We aim at identifying signaling partners responsible of acquired resistance to treatments in order to develop drug combinations to prevent resistance occurrence. Materials and methods: We engineered NETs cell lines, BON and QGP, resistant to a chemotherapeutic agent, Oxaliplatin, and to an mTor inhibitor, Everolimus, by chronically exposing them to the drugs. We are using microarray-based kinomics to obtain high throughput kinase activity profiles from drug sensitive vs resistant cells. Results: We detected high EGF receptor and SRC tyrosine kinase activities in BON cells resistant to Everolimus. In addition, in QGP cells resistant to Oxaliplatin, we noted an increased FGF receptor activity and a hyperactivation of PKCs. Hyperactivated kinases are then currently validated and assessed for their potential role in acquired resistance to the drugs. In parallel, we established kinomic profiles for NETs tumor samples. Conclusion: This method not only channels the study of kinomics from NETs cell lines, but also from tumor samples. Kinomics may then be used as a theranostic tool based on functional data from specific enzymatic activities in NETs cell lines and tumor samples. Keywords: neuroendocrine tumors, drug resistance, proteomics, kinases
PD-L1 is Expressed in a Subset of Pancreatic Neuroendocrine Tumors (pNET)

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**Introduction:** Programmed death 1 (PD-1) is an immune inhibitory receptor expressed on several immune cells, interacting with two ligands, PD-L1 and PD-L2. The former is expressed in many human cancers and is used as a selection criterion for indication of checkpoint inhibitor therapies. PD-L1 is also a potential target for checkpoint inhibitors in pNET therapy, however no data on prevalence of PD-L1 expression and potential associations to clinicopathologic features is available. **Aim(s):** As DAXX/ATRX mutated pNET have chromosomal instability, this could lead to presence or novel epitopes and increased PD-L1 expression, the inhibition of which would be a potential therapy. **Materials and methods:** We studied 117 resected pNET for PD-L1 expression by IHC (Cell Signaling, Clone E1L3N). Membranous staining using a scoring intensity (0, 1, 2) in >5% of cells was evaluated. PD-L1 expression was correlated to stage, grade, Ki-67, and presence/absence of DAXX/ATRX mutations. **Results:** 58% of primary pNET were negative (score 0), 34% were weekly to moderately positive (score 1) and 8% were strongly positive (score 2) for PD-L1, the respective rates were 54%, 38% and 8% in metastasized tumors. There was no association between PD-L1 expression and grading, stage, metastasizing potential or DAXX/ATRX loss. **Conclusion:** 42% of the primary neuroendocrine neoplasms express the PD-L1, irrespective of stage and grade. This data could indicate that checkpoint inhibition could play a role in pNET biology and be a potential therapeutic target. **Keywords:** neuroendocrine, tumors
Cytokines as Predictive Factors of Response to Somatostatin Analogues in Patients with Neuroendocrine Tumour

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Introduction: The somatostatin analogues are a major therapeutic advance in neuroendocrine tumor (NET) treatment and have multiple modulatory effects on the immune system. Aim(s): The aim of this study was to evaluate the expression of several cytokines, at baseline and after administration of lanreotide (lan), in NET patients and NET cell lines. Materials and methods: Ten NET patients were enrolled: 6 gastro-entero-pancreatic (GEP) NET, 2 bronchial carcinoids (BC), 2 breast NET. The expression of Interleukin 2, 4, 6, 10, TNF-α and IFN-γ were assessed on serum samples at T0 and after 10 up to 180 days of lan treatment, by cytometry. Lan effect on NET cell lines viability was evaluated by MTT and IL-6, IL-10 and TNF-α level by Western-Blotting. Results: In all patients, IL-2, IL-6 and IL-10 levels increased after 10 days and decreased subsequently, while IL-4 levels already decreased after 10 days. In BC and breast NET patients, IFNγ and TNFα levels were undetectable both at T0 and after lan, while in the GEP-NET these levels increased after 10 days of lan treatment and decreased subsequently. In both NET cell lines, lan treatment reduced cell viability, decreased IL-10 and increased TNF-α levels. IL-6 levels decreased in the BON-1 and increased in the NCI-H727 cells after treatment. Conclusion: Cytokines level showed a different trend in relation to the primary tumor site: GEP-NET seems to show a higher expression of Th1/Th2 cytokines and sensitivity to the immune-mediated effect of lan than BC and breast NET. Keywords: cytokines, neuroendocrine, cell
Introduction: The development of the first molecular targeted therapies for neuroendocrine tumors (NET) was a milestone in the treatment of patient. Nevertheless, these therapies eventually fail and patients become resistant to the treatment. One way of escaping this dilemma might be the combination of targeted drugs to prevent resistance development. Aim(s): The aim of the study was to assess the potency and synergistic effects of different targeted therapies in NET. Materials and methods: We studied the effect of mono- and combination therapies of the PI3K inhibitor BYL719, Hsp90 inhibitor AUY922 and mTOR inhibitor Everolimus in the human pancreatic NET cell lines BON, QGP-1 and NT-3. Signal pathway activation was analyzed by western blot. Results: Treatment of cells with monotherapy at 1nM AUY, 1µM BYL or 1nM Everolimus over 5d resulted in only minor (<10%) treatment responses. Upon combination we observed a strong synergism for Everolimus+BYL719 and AUY922+Everolimus in BON and NT-3 and to a lesser extend in QGP-1. As for a mechanism of the synergistic effects we observed, that the combination therapies modulated counter-regulatory mechanism in the tumors cells: 1) Hsp27/70 upregulation in AUY922 treated cells was prevented by the addition of Everolimus 2) Akt and Erk activation in Everolimus treated cells was abolished by BYL719 co-treatment. Conclusion: Our in vitro data strongly support the concept of combining targeted therapies in NET, that should be verified in in vivo models and ultimately tested in patients. Keywords: targeted therapies, mtor
A Role of TETs and 5-Hydroxymethylcytosine in SI-NETs

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Introduction: Small intestinal neuroendocrine tumors (SI-NETs) are rare and slow growing neoplasms. Identification of patients with worse outcome and of novel potential targets for therapy is important goals. The epigenetic mark 5-hydroxymethylcytosine (5-hmC) is severely reduced in various cancers and was recently found by us to discriminate between parathyroid adenoma and carcinoma. A growth regulatory role of TET1 was also found. Aim(s): To investigate 5-hmC level and TET protein expression in SI-NETs. Materials and methods: Here we will present results from analyzing the 5-hydroxymethylome in a total of 38 primary SI-NETs and metastases from 19 patients, by immunohistochemistry, DNA immune-dot blot, and colony forming assays. Results: Immunohistochemical staining patterns were generally heterogenous in appearance for 5-hmC and TET1, with a mixture of positive and negative cells. Aberrant TET1 downregulation might involve epigenetic mechanisms. Overexpressing TET1 in a colony formation assay with human SI-NET CNDT2.5 cells, resulted in reduced cell growth. Analysis of TET2 expression is currently under investigation. Conclusion: The result supports a growth regulatory role of TET1 in neuroendocrine tumor cells. Interestingly, quantitation of the overall 5-hmC level in the tumors by the DNA immune-dot blot assay stratified the patients into two separate clinical groups. This will be further discussed. Keywords: si-net, 5-hydroxymethylcytosine, tets
Whole-Exome Sequencing (WES) of Samples from Patients (pts) Classified as Exceptional Responders (ER) vs Poor Responders (PO) to Targeted Therapies in Pancreatic Neuroendocrine Tumours (pNETs)

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Introduction: Sunitinib (SU) and everolimus (EVE) changed the treatment landscape for patients with well-differentiated pNETs. However, no predictive biomarkers have been established for these drugs. Aim(s): We aimed to identify distinctive genomic alterations associated with benefit from SU and/or EVE treatment in patients with pNETs, by comparing ER to PO. Pts who achieved an objective radiological response together with those with a progression-free survival (PFS) beyond the median reported in the landmark trials were included in the ER group. Pts with a similar PFS to the placebo groups in the pivotal trials were classified as PO.

Materials and methods: Thirty-one pts were screened; following review of availability of the formalin-fixed paraffin embedded (FFPE) samples, 12 were found eligible to proceed with DNA extraction and sequencing. Paired DNA extracted from tumour (T) and non-T or blood was obtained. Two cases did not pass the quality check threshold for variant calling analysis (VCA).

Results: Four out of 10 patients received treatment with both drugs (EVE and SU). Overall, 10 and 3 patients received EVE and/or SU, respectively. Somatic VCA showed NBPF10, NBPF20, PKDREJ and MEN1 genes mutated in more than 1 sample. The microRNA MIR548F1 was also found altered in 2 cases. Tumours from 2 of the 3 pts classified as ER to both drugs harboured somatic mutations in MEN1.

Conclusion: It is feasible to perform WES from FFPE of phenotypically distinct pts. Our findings need further validation in larger series.

Keywords: pnets, wes, everolimus, sunitinib
Hsa-microRNA-202-3p Up-regulated in Type 1 Gastric Neuroendocrine Neoplasms

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Introduction: Type 1 gastric neuroendocrine neoplasm (g-NENs) is a kind of rare malignant tumor. The molecular mechanism of this disease is unknown. MicroRNA (miRNA) plays important roles in the occurrence and development of tumors. At present, research about the role of miRNA in type 1 g-NENs is quite few. Aim(s): To detect the abnormal expression of miRNA in type 1 g-NENs and predict its target gene. Materials and methods: The tumor tissues in 3 pts with type 1 g-NENs were taken as the experimental samples, and their gastric mucosal tissues obtained by gastroscopy were taken as the control samples. The expression of miRNAs was examined by Agilent Human miRNA chips. The expression of altered miRNA was validated by RT-PCR in 7 pts. Three target gene prediction software (TargetScan, PITA, microRNAorg) were used to predict the potential target genes of the altered miRNA. Results: Six miRNAs were up-regulated or down-regulated in the tumor as compared to the control samples. Among them, miR-202-3p was up-regulated significantly. Seven groups of RT-PCR showed miR-202-3p expression fold change were 1.07, 1.58, 1.61, 2.66, 3.94, 6.02 and 20.53 (P<0.05). 215 target genes were predicted to be associated with miR-202-3p. Among them, DUSP1 and ATP6V0A2 were reported to be closely related to gastrointestinal tumors. Conclusion: The miR-202-3p is up-regulated in lesion of type 1 g-NENs. It might play important roles in the pathogenesis of type 1 g-NENs by targeting DUSP1 and ATP6V0A2. Keywords: type 1 g-nens, mir-202-3p, up-regulated
Introduction: Neuroendocrine tumors are rare. A very little knowledge is known about its risk factors. Studies have shown that NETs may develop as a part of hereditary syndromes. Aim(s): We aim to investigate the development of neuroendocrine tumors in patients with a family history of NET or any other cancer. Materials and methods: A retrospective study was conducted in Sir Ganga Ram Hospital, Lahore. 500 patients with NET were identified and 500 healthy controls were made. Questionnaire was filled containing the data including family history of smoking and alcohol use, family history of NET and cancer and personal medical history. The study was restricted to first degree relatives only. Results: A significant relationship was seen between first-degree relatives with cancers and the development of neuroendocrine tumors especially arising at pancreas, lung, stomach and small intestine. History of oesophageal cancer in first degree relative was remarkably associated with pancreatic NETs. Cases of NETs also presented with positive family history of colorectal cancer and prostate cancer (84%). Moreover, individuals with a family history of lung cancer had a threefold increase in risk of developing pulmonary NETs. Conclusion: It has been concluded that first degree relative with any diagnosed cancer or particularly NET is a risk factor for NETs. Controls with a family history of cancer are at a risk of developing NETs. This can be explained by gene mutations, DNA methylation and chromosomal gain or loss. Keywords: genetics, nets, first degree relatives
MicroRNAs Associated with Small Bowel Neuroendocrine Tumours and Their Metastases


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Introduction: Novel molecular analytes are needed in small bowel NETs (SBNETs) to better determine disease aggressiveness and predict treatment response. **Aim(s):** To profile the global miRNome of SBNETs and identify miRNAs involved in tumour progression for use as potential biomarkers.

**Materials and methods:** Two independent miRNA profiling experiments were performed (n=90), including primary SBNETs (n=28), adjacent normal small bowel (NSB; n=14), matched lymph node (LN) metastases (n=24), normal LNs (n=7), normal liver (n=2) and liver metastases (n=15). We then evaluated potentially targeted genes by performing integrated computational analyses.

**Results:** We discovered 39 miRNAs significantly deregulated in SBNETs compared with adjacent NSB. The most upregulated (miR-204-5p, miR-7-5p and miR-375) were confirmed by qRT-PCR. Two miRNAs (miR-1 and miR-143-3p) were significantly downregulated in LN and liver metastases compared with primary tumours. We identified upregulated gene targets for miR-1 and miR-143-3p in an existing SBNET dataset, which could contribute to disease progression and show that these miRNAs directly regulate FOSB and NUAK2 oncogenes.

**Conclusion:** Our study represents the largest global miRNA profiling of SBNETs using matched primary tumour and metastatic samples. We revealed novel miRNAs deregulated during SBNET disease progression and important miRNA–mRNA interactions. These miRNAs have the potential to act as biomarkers for patient stratification and may also be able to guide treatment decisions. *(Work published)*

**Keywords:** mirna, small bowel neuroendocrine tumour
Genome-Wide Analysis of Long Non-Coding RNAs in Pancreatic Neuroendocrine Tumors by Microarray

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Introduction: LncRNAs have been shown to play important roles in cancer biology, but expression profile of LncRNAs in pancreatic neuroendocrine tumors (pNETs) is not well understood. **Aim(s):** This study was to uncover the role of LncRNA in the process of pNETs development using microarray to obtain the expression profiles of LncRNAs in pNETs and their adjacent normal tissues. **Materials and methods:** 18 pairs of pNET G1/G2 tissues were used in this study. The detection of LncRNA and transcripts was conducted using microarray analysis. Gene ontology and pathway analyses were performed to understand the biochemical function of LncRNA. qRT-PCR was performed to validate the consistency of the LncRNAs with microarray data. **Results:** Using microarray with 30,586 LncRNA and 26,109 mRNA probes, 538 LncRNAs and 437 mRNAs were expressed differentially between pNETs and adjacent normal tissues. Ten of the LncRNAs were in accordance with microarray data in qRT-PCR. Among these LncRNAs, 7 were up-regulated and 3 were down-regulated. Pathway analysis revealed that 60 pathways were correlated to the up-regulated transcripts, while 71 pathways were associated with the down-regulated transcripts. In particular, LncRNA H19 was down-regulated in all pNETs tissues. **Conclusion:** The expressions of many LncRNAs were altered in pNETs in comparison to adjacent normal tissues, suggesting that LncRNAs could potentially serve as a biomarker that is beneficial for the diagnosis and therapy of pNETs. **Keywords:** IncRNA, pancreatic neuroendocrine tumors, microarray, gene ontology analysis, pathway analysis
Genome-Wide Analysis of lncRNAs in Pancreatic Neuroendocrine Tumors by Microarray

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Introduction: LncRNAs have been shown to play important roles in cancer biology, but expression profile of lncRNAs in pancreatic neuroendocrine tumors (pNETs) is not well understood. **Aim(s):** This study was to uncover the role of IncRNA in the process of pNETs development using microarray to obtain the expression profiles of lncRNAs in pNETs and their adjacent normal tissues. **Materials and methods:** 18 pairs of pNET G1/G2 tissues were used in this study. The detection of IncRNA and transcripts was conducted using microarray analysis. Gene ontology and pathway analyses were performed to understand the biochemical function of IncRNA. qRT-PCR was performed to validate the consistency of the lncRNAs with microarray data. **Results:** Using microarray with 30,586 IncRNA and 26,109 mRNA probes, 538 IncRNAs and 437 mRNAs were expressed differentially between pNETs and adjacent normal tissues. Ten of the IncRNAs were in accordance with microarray data in qRT-PCR. Among these IncRNAs, 7 were up-regulated and 3 were down-regulated. Pathway analysis revealed that 60 pathways were correlated to the up-regulated transcripts, while 71 pathways were associated with the downregulated transcripts. In particular, lncRNA H19 was down-regulated in all pNETs tissues. **Conclusion:** The expressions of many lncRNAs were altered in pNETs in comparison to adjacent normal tissues, suggesting that IncRNAs could potentially serve as a biomarker that is beneficial for the diagnosis and therapy of pNETs. **Keywords:** lncrna, pancreatic neuroendocrine tumors, microarray, gene ontology analysis, pathway analysis.
(B8)

Nucleolin (NCL) Regulates Aerobic Glycolysis in Pancreatic Neuroendocrine Tumor (p-NET) BON-1 Cells

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Introduction: NCL, a nucleolus localized protein and ribosomal RNA (rRNA) expression regulator, has been reported to function as an oncogene in several tumors. However, the expression and role of NCL in p-NET remains unclear. Aim(s): In this study, we aimed to evaluate the expression status and function role of NCL in p-NET BON-1 cells. Materials and methods: Using Immunohistochemistry (IHC) methods, we examined the expression status of NCL in p-NET patients. We silenced NCL expression in BON-1 cells, and examined the role of NCL in BON-1 cell proliferation. To uncover the underlying molecular mechanism, we analyzed the role of NCL rRNA expression, ATP production and aerobic glycolysis. Results: NCL expression was higher in p-NET tumor samples than in matched normal paratumor samples. In vitro cell line studies demonstrated that NCL silencing inhibited proliferation, rRNA production, ATP production and aerobic glycolysis, suggesting that NCL was an oncogene in p-NET. Conclusion: Our results suggest that NCL plays an oncogenic role in the proliferation in p-NET BON-1 cells. And mechanistic study demonstrated that silencing NCL inhibited aerobic glycolysis, reduced ATP production, thus limited the expression of rRNA, which was the most energy-consuming process in cells. Thus, NCL, rRNA production and aerobic glycolysis may function as putative targets in p-NET. Keywords: pancreatic neuroendocrine tumors (p-nets), nucleolin (ncl), ribosomal rna, atp, aerobic glycolysis
Feasibility and Implication of Routine NGS Analysis in Neuroendocrine Carcinomas

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Introduction: Neuroendocrine carcinomas (NECs) may arise from any organ system, exhibit various degree of differentiation and have Ki67 indices ranging from 21-100%. After first-line platin based chemotherapy, no standard treatment exists. Aim(s): In order to further characterize NECs as well as to screen for potential eligibility for second line targeted treatment, we prospectively conducted next generation sequencing (NGS) analysis in patients with NEC. Materials and methods: Patients with NEC who were referred to the Copenhagen NET Center between Oct. 2015 and Oct. 2016, and having in-house pathological specimens available, were entered prospectively. Extracted genomic DNA was analyzed using the AmpliSeq Cancer Hotspot Lung-Colon Panel version 2 covering the most frequent hot spot mutations in 50 selected genes. Results: Forty-seven patients were eligible. NGS analysis was successful in first attempt in 43/47 (91%) patients. No mutations were found in 11/43 (26%). The most frequent mutations were: TP53 23/43 (53%), KRAS 8/43 (19%), BRAF 5/43 (12%), PIK3A 4/43 (9%), and PTEN 3/43 (7%). In-depth analysis of the correlation with primary tumor site, Ki67, CgA, and other immunohistochemical, morphological and clinical features will be presented. Conclusion: Routine NGS analysis is feasible with a high success rate. It may reveal potential drug gable targets and add further information to the characterization of NECs. Keywords: neuroendocrine, neuroendocrine neoplasms, neuroendocrine carcinoma, ngs, genes, mutation, ki67, tp53, kras, braf, pik3a, pten
High Prevalence of the c.1546delC Germline Mutation in MEN1 Pancreatic Neuroendocrine Tumors

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Introduction: Multiple endocrine neoplasia type 1 (MEN1) is an autosomal dominant disease predisposing to pancreatic neuroendocrine neoplasms (NENs). Even though its genetics is relatively well known, specific phenotype-genotype correlations remain unproven at present. The Region of Murcia in southeast Spain is one of the areas with the highest incidence of MEN1.

Aim(s): The characterization of germline mutations in the MEN1 gene in patients with pancreatic NENs.

Materials and methods: Patients with pancreatic NENs treated between 1983-2015 at a single center were included (n=85). Family/personal history was collected. Germline DNA was analyzed from peripheral blood. MEN1 gene sequencing was carried out on exons and adjacent regions to identify mutations.

Results: Five different germline MEN1 mutations were detected in 21 out of 85 patients with pancreatic NENs: c.1546delC, c.1541delC, c.1715_1730del, c.599delG and c.960dupC. The presence of the c.1546delC mutation (exon 10) in 77.27% is remarkable. The frequency of the remaining mutations was lower (a single case for each, 4.55%). All hereditary pancreatic NENs presented with hyperparathyroidism, most of them were diagnosed at non-metastatic stages (96%), and presented less aggressive biological characteristics and greater overall survival, compared to sporadic NENs (p=0.02)

Conclusion: The inherited mutation c.1546delC is frequent in patients with MEN1 pancreatic NENs. The clinical relevance and role of this mutation in tumorigenesis of pancreatic NENs should be further investigated.

Keywords: men1 genetics
Genetic Features and Immunoprofile of Sporadic Well-Differentiated Neuroendocrine Tumors of Gastric

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Introduction: Well-differentiated Type III gastric neuroendocrine tumors (gNET III) are histologically distinct subset that has a unique pathogenesis and clinical course. Aim(s): To further evaluate the genetic, pathological, and clinical features of gNET III. Materials and methods: We analyzed the expression of Ki67, SSTR2/5 in gNET III in relation to alterations in the PI3K-Akt pathway, TP53 status (p53/Rb immunohistochemistry) and ALT were detected (ATRX, DAXX). Fisher’s exact test and X2 was performed. Results: The median patient age was 62 (range 42~85 y). Ki67 index was 5% in average frame (1%~40%. G1 35%, G2 50%, G3 15 %. Median follow-up 53 months (range 10~123 months), 3 showed local LN metastases and 3 distant metastases ( liver and bone). None was died of disease, 14 pts (70%) were alive with no evidence of disease. Recurrence and/or metastases was strongly associated with tumor size > median size (2cm), mitotic activity greater than 5/10HPF, Ki67 index > 10%, and necrosis. Immunohistochemically, Both of ATRX and DAXX were positive in 16 cases, both negative in 2 cases, indicated no CIN in gNET III cases, and was confirmed with ALT FISH. P53 or Rb aberrant expression was found in seven cases, while SSTR2/5 highly expression was detected in 16 cases. One had NRAS mutation (G61A), and one had ALT. KRAS, PIK3CA, and B-catenin mutation was not present. Conclusion: Type III NET of gastric may be classified as intermediate malignancy. Its genetic feature may be different from pancreas, small intestinal NET and PDNEC. Keywords: genetic, wdnet.
The Effect of the Autophagy Inhibitor Chloroquine (CQ), Alone or in Combination with mTOR Inhibitors, on Neuroendocrine Tumor (NET) Growth and Metastatic Spread in Mouse Models

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Introduction: mTOR inhibitors (mTORi) such as RAD001 demonstrated promising anti-cancer effect in NETs. Autophagy, a cell survival mechanism, is activated by mTORi. We have recently shown in the human NET cell line BON1 that autophagy is essential for cell survival. Treatment with CQ alone or together with mTORi robustly inhibited cell proliferation and survival, suggesting that treatment with CQ may potentiate the anti-tumorigenic effects of mTORi. Aim(s): To examine the possible anti-proliferative effects of these drugs in three in vivo NET mouse models. Materials and methods: We utilize three mice ex vivo models: BON1 subcutaneous xenografts, BON1 liver metastasis, and a human NET subcutaneous transplantation. Results: In the BON1 xenograft mice model, CQ alone but mainly in combination with RAD001 significantly decreased the average tumor volume (620mm3 and 113mm3, respectively). Histopathological analysis revealed that CQ caused an increase in tumor LC3 levels (an autophagy marker) while in combination with RAD001 the increase in LC3 was even more marked (mean fluorescence intensity (MFI) of 6.7 and 14.5 respectively), suggesting inhibition of autophagy in these tumors. CQ induced tumor cell apoptosis (by TUNEL analysis), both alone and mainly in combination with RAD001 (MFI of 5.5 and 8.2 respectively). Conclusion: These preliminary results suggest a favourable effect for chloroquine, alone and mainly in combination with mTORi, in suppressing NET growth in the BON1 subcutaneous xenograft model by inducing apoptosis. Keywords: autophagy, mtori, net
Potential Anti-Tumor Activity of Biguanides and Statins in Neuroendocrine Tumor Cells

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Introduction: Recent studies have suggested that biguanides and statins have beneficial effects on various cancer types; however, the precise effects and the molecular mechanisms underlying this pathophysiological association are still not well understood in neuroendocrine tumor (NETs). Aim(s): To investigate the potential effects of different biguanides and statins on NETs. Materials and methods: Proliferation, migration, secretion and gene expression in BON1/QGP1 cells. Results: Metformin, buphormin and phenformin significantly decreased proliferation rate in both NET cell-types (at 24/48/72h). However, the effects of statins on proliferation rate were statin-type, cell-type and time dependent. Specifically, only simvastatin/atorvastatin decreased proliferation rate in BON1 cells (48/72h and 48h, respectively) while, all statins decreased proliferation rate in QGP1 cells (simvastatin, atorvastatin and lovastatin at 72h; rosuvastatin at 48/72h). Remarkably, metformin and simvastatin also decreased migration capacity in BON1 cells and, some biguanides and statins reduced serotonin secretion in NET cells. These antitumor effects were likely mediated by altered expression of key genes involved cancer aggressiveness (i.e. Ki-67, pttg, p53, insulin-R, etc.). Conclusion: Taken together, our results reveal a clear inhibitory effect of biguanides and statins on NET cell aggressiveness, and given their demonstrated clinical safety suggest a potential therapeutic role of these compounds for the treatment of patients with NETs. Keywords: nets, biguanides, statins

Neuroendocrinology 2017;105(suppl 1): 1-338
Introduction: The lack of adequate in vitro and in vivo preclinical models has hampered the identification of novel treatment options and the development of personalized therapy selection for pNET patients. **Aim(s):** to establish 3D culture of primary pNETs, which are viable, metabolic active and phenotypically comparable to the tumor of origin for several days after isolation. **Materials and methods:** Cells are isolated from pNET specimens and cultivated for 12-15 days. Treatments start at day 3 and last until day 9-10. Growth and cell viability are monitored until the end of the experiment. Spheroids are fixed and embedded in paraffin for IHC staining on proliferation, cell death and specific neuroendocrine phenotypic markers, for comparison to the original tumor tissue. **Results:** After 3 days in culture proper tumor spheroids or 3D islet like structure are formed. Isolated cells are alive and metabolic active until day 12-15, retaining expression of endocrine markers CgA and SynA and hormone as well as proliferation rate comparable to the original tumor. We are able to treat cells up to 9-10 days in culture and record big differences between responding and not-responding samples. We found significant differences in response between 3 and 6 days of treatment, indicating that long treatment data may be relevant. **Conclusion:** 3D culture of primary pNET is a robust and promising new preclinical model to study pNET and may be exploited to test novel treatments and possibly to predict patient therapy response. **Keywords:** pnet, preclinical models, 3d culture.
Influence of VEGF Splicing on Microvessel Density and Architecture in Pancreatic Neuroendocrine Tumours

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Introduction: Hypoxia in human tumours is associated with a poor prognosis and is characterized by the stabilization of HIF1\(\alpha\), upregulation of VEGF, and a high microvessel density (MVD). Interestingly, although pancreatic neuroendocrine tumours (pNETS) showing hypoxia signalling also have a poor prognosis, they paradoxically display a low MVD. We hypothesized that this paradoxon might be explained by alternative splicing of VEGF. Aim(s): Our aim was to analyze the microvessel architecture in pNETs with high and low MVD and to investigate the role of VEGF-A splicing in these tumours as well as in the human pNET cell lines Bon1 and QGP1. Materials and methods: In each five pNETs with high and low MVD microvessel architecture was examined using 3D reconstruction. VEGF-A splicing was examined in the same tumours as well as in Bon1 and QGP1 under normoxic and hypoxic conditions. Results: pNETs with low MVD in 3D reconstruction displayed a disturbed vessel architecture. In human tissues, a progressive decrease in the expression of all VEGF isoforms with a shift towards the anti-angiogenic isoform VEGF121 was observed from normal islets over pNETs with high MVD to pNETs with low MVD. Similarly, the human pNET cell line QGP1 showed a shift towards the expression of the antiangiogenic isoform VEGF121a under hypoxic conditions. Conclusion: Differential splicing of VEGF with a relative switch to the isoform VEGF121 seems to contribute to the paradoxical low MVD and the aberrant microvessel architecture in pNETs showing hypoxia signalling. Keywords: pnet, vegf
CALM-NET, A Multicentre, Exploratory Study to Assess the Clinical Value of Circulating Tumour Cells (CTCs) Enumeration in Patients (Pts) with Functioning Midgut NETs Receiving Lanreotide Autogel (LAN)

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Introduction: The presence of CTCs confers adverse prognosis in metastatic NET pts with heterogenous treatment history. Post treatment CTC count correlates with disease progression and overall survival. **Aim(s):** CALM-NET (NCT02075606) investigates the benefit of enumerating CTCs to predict symptom control in midgut NET pts on LAN. **Materials and methods:** This study enrolled 50 pts with somatostatin receptor positive, functioning midgut G1/G2 NET. Pts were not permitted to receive interferon, chemotherapy, chemoembolisation or radionuclide therapy within 3 mo of study entry; prior somatostatin analogue treatment was permitted but after washout. Pts receive LAN at a starting dose of 120mg/28d; after 3 injections, dose can be maintained or down-titrated to 60 or 90mg/28d for remainder of the study. CTC levels are measured at 1, 5, 17, 25 & 53wks, and pts report on symptom control. Frequency/severity of symptoms are taken daily in the first 16wks, on days 11-17 for subsequent injections and days 11-28 after wk49. CT/MRI scans are used to assess progression at wks25 & 53. Impact on quality of life is assessed via the EORTC QLQ-NET21 and QLQ-C30. **Results:** Results will examine the relationship between CTC presence and clinical symptom response (defined as ≥50% decrease in average no. of symptoms, or a decrease of mode severity by ≥ one level between baseline and end of study). **Conclusion:** CALM-NET will provide evidence on CTC clinical use in a relatively homogenous group of LAN-treated midgut NET pts. Industry sponsored. **Keywords:** midgut neuroendocrine tumor, ctc, lanreotide
Introduction: Neuroendocrine tumors (NETs) overexpress CXCR4. We have previously shown that stimulation of CXCR4 by its ligand SDF-1 promotes the epithelial-mesenchymal transition (EMT) and increases distant tumor spread. Ulocuplumab (Ulo) is a fully human IgG4 mAb designed to inhibit the binding of CXCR4 to SDF-1. Aim(s): We investigated the effect of CXCR4 inhibition in preventing pNET spreading in vitro. Materials and methods: Complement-dependent cytotoxicity (CDC), Ab-dependent cell cytotoxicity (ADCC), Ab-dependent cell phagocytosis (ADCP) and direct Ab-induced apoptosis were investigated in vitro using three pNET cell lines (BON1, CM, QGP1) treated with Ulo. Following their incubation with SDF-1, RNAseq was used to profile the transcriptome before and after treatment with the mAb. The effects of Ulo on pNET cell morphology, as well as migration and invasion towards liver and bone fragments were also studied. Results: Ulo failed to induce CDC, ADCC, ADCP and direct tumor cell killing in pNET cell lines. Ligand stimulation of CXCR4 promoted an EMT-like transcriptional shift, which was abrogated by Ulo. By confocal microscopy, Ulo prevented the acquisition of features suggestive of SDF-1-induced EMT. Both migration and invasion of pNET cells towards liver and bone in vitro were significantly suppressed by CXCR4 blockade. Conclusion: Ulo appears ineffective in promoting direct anti-pNET cytotoxicity. However, its inhibitory activity on EMT might be of potential therapeutic interest in pNETs. Keywords: pnet, cxcr4, emt, ulocuplumab
Establishment of the First Well-Differentiated in Vivo Human Pancreatic Neuroendocrine Tumor Model

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Introduction: The development of new therapeutic strategies for cancer patients relies on in vitro and in vivo testing of novel substances in the preclinical setting. So far, this has not been possible for pancreatic neuroendocrine tumors (pNET) due to lack of suitable animal models resembling the disease course in human patients. Aim(s): The aim of the study was to establish a new animal model for pNETs. Materials and methods: We subcutaneously transplanted tumor cells of the recently created well-differentiated human pancreatic neuroendocrine tumor cell line NT-3 into the flanks of NOD/SCID mice. Results: Tumors developed in transplanted mice with a high tumor take rate (15 of 16). In contrast to xenograft models of BON and QGP-1 cells the NT-3 xenografts grew slowly with a doubling time of more than 3 weeks (+239%/4 weeks). The ensuing tumors displayed the same histological features as the original human tumor and had a Ki-67 labelling frequency of 15-20%. qPCR analysis showed high expression of somatostatin receptors 1, 2, 3, and 5. Furthermore, high levels of human insulin in the blood of transplanted animals confirmed functionality. Conclusion: We here report the first human pancreatic neuroendocrine tumor animal model with a well-differentiated phenotype. Given the slow growth rate and the high level expression of somatostatin receptors, this model will prove to be a hitherto unavailable tool to further improve treatment strategies for neuroendocrine tumors. Keywords: pnet, insulinoma, sstr
Introduction: Colorectal cancer is the third most common cancer in the UK this had led to development of the bowel cancer screening programmes (BCSPs). There are few epidemiological data on rectal or ileal NETs diagnosed in BCSPs. Aim(s): This study aims to identify the number of NETs diagnosed through the UK BCSP. Materials and methods: UK bowel cancer colonoscopy data is stored on the Exeter database managed by Public Health England (PHE). Queries were developed by PHE to capture potential NET related search terms across relevant data tables in the Exeter database. Queries were run to identify BCSP participants attending for colonoscopy from 2006 to December 2014. A written proforma was sent to the responsible BCSP clinician for all participants identified with NET related search terms. Results: 216707 participants had colonoscopies. There were 146 unique BCSP participants with NET related codes. 60% of the 146 participants were male (n=87). Primary sites: colorectal region (n=102, 70%), ileum (n=24, 16%), unknown (n=18, 12%) and appendix (n=2, 1%). The incidence of ileo-colonic NETs was 67 per 100,000 colonoscopies per year. Grade 1=85% (83/98); 8% grade 2 (8/98) and 7% grade 3 (7/98). Metastases were present in 24% of cases (23/95). 94% (102/108) were discussed in a multidisciplinary meeting (MDM). Additional recommendations were made in 82% of instances (63/77). Conclusion: This is the first data reporting on incidence of ileo-colonic NETs within BCSP. It provides evidence of early stage of disease at presentation of NETs. Keywords: screening
Quality of Life, Anxiety and Depression in Patients with NEN after Surgery

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Introduction: Less is known about quality of life and psychiatric disorders in surgical cohort of NEN patients (pts.). Aim(s): To elucidate the need for psychiatric therapy and support in NEN pts. Materials and methods: Patients treated in the department of surgery for NEN were offered a programmed follow-up. The questionnaire contained quality of life (qol, SF-36, EORTC-/GI NET 21), anxiety and depression scale (HADS-D) and a third part developed locally. Patients with 2 or more questionnaires were included (n=90). Time scale was defined as T1, T2, T3 and T4 (within 1, 2, 5 or more than 5 years after surgery). Results: 11,6% suffer of a psychiatric disorder at initial diagnosis. 50% reported a critical life event within 5 years before diagnosis of NEN. 82% had a complete tumor resection. Qol is worsening in all items except surgery related symptoms from T1-T4. Pathologic finding for depression was seen in 17, 27, 42 and 33%, for anxiety in 19, 23, 26 and 8% of pts. from T1-T4. Conclusion: The prevalence of psychiatric disorders is elevated in NEN pts. QOL is impaired, anxiety and depression remain a problem even after curative treatment. More support and psychiatric diagnostic and therapy should be offered to all NEN pts. Keywords: surgery, qol, anxiety, depression
Multicenter Analysis of the Clinicopathological Characteristics and Prognosis of Colonic Neuroendocrine Neoplasms

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Introduction: Neuroendocrine neoplasms (NEN) arising from colon is rare. Few studies investigate the clinicopathological features and prognosis of colonic NEN. **Aim(s):** To investigate the clinicopathological characteristics and their relationship with prognosis of colonic NEN in Chinese patients. **Materials and methods:** Medical records of patients with colonic NEN diagnosed from June 2001 to July 2016 were retrieved from six hospitals respectively located in north, east and south of China. **Results:** 44 patients including 22 males were included. The median age was 58.8 years (23-83 years). Most of the colonic NEN originated in hindgut (54.5%), and 47.8% of patients had stage IV disease. Only 25.0% of colonic NEN were well differentiated neuroendocrine tumor. 59.1% and 15.9% of colonic NEN were poorly differentiated neuroendocrine carcinoma and mixed adenoendocrine carcinoma respectively. 15.9%, 6.8% and 77.3% of patients had grade 1, grade 2 and grade 3 disease respectively. Abdominal pain was the most common symptom while ulcerative or cauliflower-like tumors were the most common appearance under endoscopy. The 3-year overall survival rate was 45.7% (95%CI, 36.5%-54.9%). Multivariate analysis showed that stage IV was an independent factor indicating poor prognosis. **Conclusion:** Colonic NEN is rare and poorly differentiated NEN is more common. The prognosis of colonic NEN patients is unfavorable. **Keywords:** colon, neuroendocrine neoplasms, clinicopathological features, prognosis
Introduction: Small intestinal NEN (SI-NEN) is much rarer in Asian countries. Hence, the clinicopathological characteristics of SI-NEN are still unknown in Asian population. **Aim(s):** To investigate the clinicopathological features of SI-NEN in Chinese patients. **Materials and methods:** Clinical data of 277 patients with SI-NEN were retrieved from eleven hospitals respectively located in north, middle, west, east and south of China. Kaplan-Meier analysis was applied to evaluate the overall survival of SI-NEN patients. **Results:** The mean age of patients was 54.4 years (95%CI, 52.8-56.0). Duodenal NEN was much more common (76.5%). The most common symptom was abdominal pain (54.9%) while carcinoid syndrome was much rarer. 36.5%, 32.5% and 30.9% of patients had grade 1, grade 2 and grade 3 disease respectively. 24.9% of patients manifested advanced disease. The 5-year overall survival rate of patients with SI-NEN was 67.7% (95%CI, 59.3% to 76.1%). Duodenal NEN tended to be smaller compared with jejunooileal NEN (2.6 cm vs. 3.6 cm; P<0.001). T1/T2, N0, stage I/stage II were significantly more common in duodenal NEN. **Conclusion:** The clinicopathological features of SI-NEN in Chinese population are quite different from that in western population. Duodenal NEN is more common and NEN from duodenum and jejunooileum harbor different features. **Keywords:** small intestine, neuroendocrine neoplasms, clinicopathological features
The Clinicopathological Characteristics and Prognosis of Rectal Neuroendocrine Neoplasms: A Multicenter Retrospective Study from China

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Introduction: Rectum is one of the most common primary sites of neuroendocrine neoplasms (NEN). But few studies from China with large sample investigated the clinicopathological characteristics of rectal NEN. Aim(s): To investigate the clinicopathological features and their relationship with prognosis of rectal NEN in Chinese patients. Materials and methods: Medical records of patients with rectal NEN diagnosed from June 2001 to September 2016 were retrieved from three Chinese hospitals. Results: 291 patients were included. Male patients were more common (62.9%). The median age at diagnosis was 47.5 years (range: 15-92 years). Stage I tumor accounted for the most proportion (68.7%). 92.8% of tumors were well differentiated. 73.9%, 18.9% and 7.2% of patients had grade 1, grade 2 and grade 3 disease. Changes of the characteristics or habits of stool were the most common symptoms (24.7%). Most of the G1/G2 tumors were submucosal tumor (67.9% and 32.7% respectively) while most of the G3 tumors were cauliflower-like (66.7%). The 3-year survival rate of patients was 94.3% (95%CI, 92.4% to 96.2%). Multivariate survival analysis revealed that poor differentiated tumor was an independent risk factor of poor prognosis. Conclusion: Most of rectal NEN are well differentiated and the prognosis of most of the patients is favorable. Tumors with different grade display different endoscopic appearance. Keywords: rectum, neuroendocrine neoplasm, clinicopathological features, prognosis
Introduction: Knowledge about gastroenteropancreatic neuroendocrine carcinomas (GEP-NEC) is scarce given their low incidence rates and aggressive clinical behavior. Aim(s): To characterize the epidemiology and outcomes of GEP-NECs. Materials and methods: The Surveillance, Epidemiology, and End Results (SEER) database was used to identify GEP-NECs during 1973-2012. Associated population data were used for incidence analyses. Results: We identified 6291 GEP-NEC cases. The lower gastrointestinal tract (colon, rectum and anus) accounted for 38%, the upper gastrointestinal tract (esophagus and stomach) and the pancreas for 23% each. Incidence rates of GEP-NECs have steadily increased from 1.5 per million in 1973 to 4.6 per million in 2012. Small cell morphology accounted for 34% of all GEP-NEC. Esophagus and anal NEC had predominantly small cell morphology. Distant stage at diagnosis ranged from 40% (anal) to 76% (pancreas). Median survival for all GEP-NEC was 6.5 months, m (range: 4.1 m for pancreas to 21.7 m for small intestine). 5-year survival for local stage GEP-NEC was 39.7% (range 21.3% for esophagus to 56.1% for rectum). Primary site remained highly statistically significant for survival even after adjusting for known prognostic variables. Conclusion: We observed significant differences in incidence trends over time and large variations in survival depending on anatomical site and morphological subtype of GEP-NECs. A curative approach is possible for a substantial proportion of patients with localized or regional stage.

Keywords: grade 3, neuroendocrine carcinoma
Report on the Clinicopathological Characteristics of 548 Romanian Patients with Neuroendocrine Tumors Treated with Somatostatin Analogs

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Introduction: In Romania, treatment with somatostatin analogs (SSA) for neuroendocrine tumors (NETs) is based on the National Clinical Practice Guideline for the Diagnostic and Treatment of NETs and is reimbursed by the National Health Insurance Company since 2008. Aim(s): We reviewed the database of Romanian patients with NETs that received reimbursed SSA between 2008 and 2015 in order to describe their characteristics. Materials and methods: The National Health Insurance Company approved access to the database. Results: We recorded 548 patients, with a mean age of 57.66±12.16 years, of which 46.7% were women. The most common primary sites were gastroenteropancreatic (GEP) system (52.9%) and lung (22.8%). At diagnosis systemic metastases with unknown primary origin were present in 14.8% patients. Based on Ki 67 and WHO 2010 classification there were 41.4% G1, 38.9% G2 and 19.7% G3 GEP-NETs. Carcinoid syndrome was present in 68.8% patients and 75.9% patients had local or distant metastasis at diagnosis. All patients received treatment with SSA, 5.3% in association with interferon, 47.8% with chemotherapy or molecular targeted therapies and 8.8% radiotherapy. At the end of 2015, 29.2% (45% GEP-NETs, 28.7% lung and 16.3% unknown primary, 71.6% carcinoid syndrome, 86.9% metastasis) patients were deceased. Conclusion: This is to our knowledge the first Romanian study providing information regarding the clinicopathological characteristics of NET patients receiving reimbursed somatostatin analogs. Keywords: neuroendocrine tumors, somatostatin analogs
Management of Neuroendocrine Tumors in the Netherlands

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Introduction: To determine optimal management of patients with pancreatic neuroendocrine tumors (pNETs), more insight in the prognosis and treatment outcomes is needed. Aim(s): To present an overview of pNET management in the Netherlands. Materials and methods: Through a nationwide registry, patients with pNET between 2008-2013 in the Netherlands were retrospectively analyzed. Results: In total, 614 patients were included, 261 patients died. Median follow-up was 25.7 months. Lymph node metastases were seen in 178 (29%), distant metastases in 289 (47%) patients. Five-year survival was 79% with and 27% without distant metastases (p<0.001). The effect of distant metastases on survival was more evident in lower tumor stages (T1-2 p<0.001, T3 p=0.019, T4 p=0.11). Resection in case of metastatic disease showed better survival compared to systemic treatment (87% vs 28%, p=0.004). Without surgery, patients with advanced disease had better survival with systemic treatment than without any treatment (28% vs 15%, p=0.015); independent of tumor stage (T1-2 vs T3-4, p<0.001). Tumor grade and stage was associated with worse survival. Nodal status in did not have an influence on survival, independent of distant metastasis, tumor stage or tumor grade (p>0.05). Conclusion: Distant metastasis, tumor stage and tumor grade affect survival. The effect of distant metastasis on survival is reduced with advanced tumor stage. In the presence of distant metastasis, resection and systemic treatment show better survival. Keywords: pnet, netherlands, management, national registry
Ecological Study to Assess the Management of Gastroenteropancreatic Neuroendocrine Tumors in Spain

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Introduction: Neuroendocrine tumors (NET) have widely varying characteristics, localizations, and treatments. Consequently, a multidisciplinary approach to diagnosis and treatment is necessary. Given the heterogeneous management of this disease, we conducted an ecological survey to assess usual clinical practice in Spain. Aim(s): To describe tumor characteristics of patients and usual treatment approach of surveyed clinicians. Materials and methods: Survey (46 questions) of 19 oncologists specializing in the treatment of NETs. Data reported as means (standard deviation). Results: Most respondents (12; 63.2%) were employed at large hospitals (>400 beds). Gastrointestinal (GI) NETs account for 41.3%(±17) of cases, followed by pancreatic NETs in 39.5% (±16.3). Pathological reports are available in 98.5%(±4.6) of cases, Ki-67 in 92.5% (±9.9), and octreoscan in 80.4%(±21.4). Most cases (62.8%(±29.4)) are presented to a multidisciplinary tumor board before treatment. Respondents estimated that most pancreatic tumors (70.3%(±14.2)) are stable or slowly progressive (>6 months) and most nonfunctioning (76.1%(±14.5)). Most GI tumors are stable or slowly progressing (79.7%(±10.7)) and nonfunctioning (59.6%(±30.9)). The "wait-and-watch" approach is a first line treatment alternative in 15.0%(±15.5) of G1 pancreatic tumors and 20.5%(±21.8) of G1 GI tumors. Conclusion: These findings shed light on the characteristics and management of gastroenteropancreatic NETs in Spain. Industry sponsored. Keywords: gastrointestinal, neuroendocrine, pancreatic tumors, survey, spain
Neuroendocrine Tumors Committee of Reference Hospital: Evaluation of Health Care and Research Indicators


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Introduction: Neuroendocrine tumors (NETs) require a multidisciplinary approach in expert centers which optimize results improving care and survival. Aim(s): To evaluate a set of established health care and research indicators. Materials and methods: The indicators were selected from those established by Spanish Society of Medical Oncology (SEOM) and were evaluated before (2013) and a year after (2015) the establishment of a multidisciplinary NET committee. Results: The multidisciplinary team meets monthly and is made up of: biochemists, endocrinologists, gastroenterologists, nuclear medicine doctors, oncologists, pathologists, radiologists and surgeons. Comparing the health care activity from 2015 to 2013, the indicators show a reduction in: median time and number of visits between the 1st consultation and the 1st treatment (74 vs 127 days and 2 vs 6 visits), number of diagnostic studies (4 vs 9) and more administration of specific therapies (7 vs 1 locoregional hepatic treatments). The research activity of the committee in 2015 includes: a funded study, participation in the national register of TNE (RGETNE) with the inclusion of 316 patients, development of a protocol of NET, 4 international and 3 national conference presentations and collaboration in 5 clinical trials. Conclusion: The establishment of a NET committee has allowed to optimize the resources, reduce the times, indicate more specific treatments and participate in research projects, mostly of the Spanish Group of NET (GETNE). Keywords: committee, indicator, multidisciplinary, resource
International Patient Survey of Physical, Emotional and Informational Challenges when Living with NETs: Understanding the Unmet Needs

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Introduction: The usefulness of information sources used by NET patients is rarely explored by patient surveys of disease burden/impact on daily living, and may be key to optimizing care. Aim(s): Identify unmet needs/possible solutions for information/support to address NET patients’ physical, emotional and informational challenges. Materials and methods: The Carcinoid Cancer Foundation (CCF), Netzwerk Neuroendokrine Tumoren (NeT) e.V. and Association de Patients porteurs de Tumeurs Endocrines Diverses (APTED) approved questions; patients registered with the respective websites were emailed links. Results: 741 online surveys (12–13 questions) were completed in the USA (n=428), Germany (n=240) and France (n=73) over 6 weeks in 2015. ≥65% of patients were diagnosed ≤5 years ago. Multiple symptoms can occur, most commonly diarrhea (40% min–47% max) and flushing (29–45%). Most common emotions upon diagnosis: anxiety (20–67%) and fear (14–58%). Greatest physical challenges: fatigue (26–66%), diarrhea (20–48%), pain/discomfort (13–40%), and sleep disturbance (16–36%). “Very useful” information sources included patient association websites, disease awareness websites and journals; “patients-like-me” case studies were most favored (43–68%) for future use. Country nuances exist. Conclusion: NET patients need psychological support/coping strategies and seek reliable, personally relevant, easily understood information. Such information helps them face negative emotions worsened by multiple physical challenges. Keywords: net, patients, survey, symptoms, unmet needs
Introduction: Bronchopulmonary carcinoids (BC) represent 1% of lung cancers and comprise typical (TC), atypical carcinoids (AC), small cell lung cancer (SCLC) and large cell cancer. **Aim(s):** We present characteristics of patients with TC, AC, SCLC, LC, carcinoid and neuroendocrine cancer referred to Moscow Cancer Centre between 1989 – 2016 years. **Materials and methods:** Retrospective analysis of 231 BNETs from the data base (1989 – 2016) using the medical records of pts. The overall number of BNETS per year was insignificantly increasing: 1980-1989 –28pts, 2010-19, 2014–22pts. **Results:** We included 231 pts in our registry from different regions of Russia, there were 115women (49.8%) and 116 men (50.2%), comprising 27.3%. Mean age was 49.6 for women, 52.9 years for men. 38 pts were diagnosed with TC (16.5%), 51 pts with AC (22.1%), 43pts with SCLC (18.6%), and 11 pts with LC (4.8%). Besides that there were 79 pts with carcinoid (34.2%), 8 pts with neuroendocrine cancer (3.58%) and no data – 0.4%. Localized tumors were in 80 pts (34.6%), locally advanced stages in 23 (10.0%) and advanced stages in 98 pts (42.4%) out of 231 patients. No data concerning 30 pts (13.0%). The overall 1 year survival of pts with TC and AC was 100%, SCLC-85.7%, LC–100%, Carcinoids–95.9%, neuroendocrine cancer – 100%. Five year survival: for TC-100%, AC-96.3%, SCLC–85.7%, LC-100%, Carcinoid – 80.3%, for neuroendocrine cancer–100% **Conclusion:** Parameters as demographic, clinical, histopathological and diagnostic data were collected for BNETS and analyzed. **Keywords:** registry, lung
Treatment Patterns and Survival Among Patients with Metastatic Gastroenteropancreatic Neuroendocrine Tumours in Sweden – A Population-Based Register-Linkage and Medical Chart Review Study

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Introduction: Gastroenteropancreatic neuroendocrine tumours (GEP-NETs) is a group of neoplasms derived from the endocrine system in the GI tract and pancreas. Aim(s): To describe treatment patterns and survival among patients with metastatic GEP-NET grade 1 or 2 in Sweden. Materials and methods: Patients diagnosed with metastatic GEP-NET grade 1 or 2 in 2005-2013 in Sweden were included (n=811; national population). Data was obtained via linkage of several nationwide registers. For the subpopulation diagnosed at Sahlgrenska University Hospital, Gothenburg (n=127; regional population), medical charts were reviewed. Treatment patterns and survival were assessed. Results: Most patients had small intestinal NET (76%). In the regional population, 72% had a grade 1 tumour; 50% had functioning tumours. In the national population, surgery was the most common first-line treatment (57%), performed in average 26 (95% CI 20-32) days after diagnosis. After first-line surgery, 46% received SSA, while 40% had no further treatment. Overall median survival time from date of diagnosis was 7.0 years (95% CI 6.2-not reached). Among patients with distant metastases, pancreatic NET (vs. small intestinal NET) was associated with poorer survival (HR 1.9; 95% CI 1.1-3.3), as were liver metastases (HR 3.2; 95% CI 1.5-7.0). Conclusion: First-line surgery was typically followed by SSA or no further treatment. Among patients with distant metastases, pancreatic NET or liver metastases were associated with a poorer survival. Keywords: gep-net, ssa, treatment patterns, survival

Neuroendocrinology 2017;105(suppl 1): 1-338
Establishment of Japan NeuroEndocrine Tumor Society and Its Registration System


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Introduction: In 2012, many nation-wide gastroenterologists, endocrinologists, surgeons, radiologists and pathologists have established Japan NeuroEndocrine Tumor Society (JNETS) in Japan. JNETS is now composed of 304 institutes. Aim(s): One of the activities of this society include establishing the registry system for NET patients to understand the current status of NET patients in Japan toward the revision of the guideline. Materials and methods: The NET registry system has been contracted to TRI, the 3rd party institute outside of JNETS with the financial support from JNETS. The JNETS members register the patients diagnosed as pancreatic, gastrointestinal, or lung/thoracic NET after 2012 with opt-in consent, starting on January 2015. The data registered in this system are examined by JNETS members to resolve clinical questions for NET disease in Japan. Results: By October 2016, 604 patients have been registered in this system. At this juncture, the most frequent age groups of the patients are 60s. Male and female are 51.4% and 48.6% of the total patients, respectively. Fourteen percent are functional and those with hereditary background were 4.8%. Approximately 20% of the NEC was well differentiated (proposed NET G3 in WHO Classification 2017). Conclusion: This is the first registration system of NET established in Japan. This system should greatly contribute to understanding the current status of medical care of the patients and to establishing the more evidence-based guideline of Japanese NET patients. Keywords: registry system, japan,
Epidemiology of Carcinoid Heart Disease (CHD) in Patients (pts) with Carcinoid Syndrome (CS): A Systematic Literature Review

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Introduction: CHD develops in the context of CS due to the exposure of high levels of vasoactive substances, such as serotonin. Aim(s): This review reports CHD among CS pts epidemiology outcomes. Materials and methods: A systematic literature search was performed in PubMed, Embase, Cochrane Library and ClinicalTrials.gov. Study type, patient characteristics and epidemiological outcomes were collected. Results: Reported prevalence of CHD in CS varied from 16 to 28% but rises at 40-85% in cohorts of CS pts referred for echocardiography because of suspected CHD. CHD is an independent negative prognostic factor for CS pts survival. In pts with small intestine NETs, 5 year overall survival is 37% for pts with CHD and 71% for non-CHD pts. CHD pts had higher mortality and morbidity vs non-CHD pts. Perioperative valvular surgery mortality remains consistently at 15-20%. When pts survived, acceptable outcomes and better functional status were achieved. Long-term survival of CHD pts undergoing valve replacement is determined by tumour progression. Conclusion: It is likely that 15-30% of CS pts develop CHD rather than the 20-70% usual estimate. Over the past decades, progress in the management of CS and CHD has increased pts’ survival. However, the understanding of CHD epidemiology and trends remains limited due to small numbers of pts. A registry for CS with harmonized CHD data could facilitate further research. Industry sponsored. Keywords: carcinoid syndrome, heart disease, epidemiology, prevalence, mortality
What Do We Know About Carcinoid Heart Disease? A Systematic Literature Review

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Introduction: Carcinoid heart disease (CHD) is a life-threatening complication of carcinoid syndrome (CS). Aim(s): Our aim was to review published findings for CHD. Materials and methods: A systematic literature review was conducted focusing on Europe and North America, without date restrictions. After de-duplication, 380 records were retrieved and screened, of which 39 were selected for data extraction (EU n=21, US n= 18). Results: No CHD-specific trials were found. Observed CHD patient sample sizes varied from 7 to 265 (median US 65, EU 27) with study periods ranging from 1 to 28 years (median US 20y, EU 5y). CHD patients have significantly increased levels of urinary 5-hydroxyindoleacetic acid (5-HIAA) levels compared to non-CHD CS on average 2-4 fold higher respectively. Peak 5-HIAA levels were linked to CHD progression (odds ratio, 1.08 for each increase of 25 mg per 24 hours). Increasing proportion of patients are receiving valvular surgery (25% in 1989, 47% in 2008). CHD outcomes have improved over time with greater use of somatostatin analogues, hepatic artery embolization, better perioperative management and surgery outcomes. Conclusion: Reporting of CHD outcomes are inconsistent, and visibility is low. Research faces limitations: lack of clinical studies, poor feasibility of randomised trials, lack of standardized criteria for quantifying CHD progression. More international collaboration is needed. Industry sponsored. Keywords: carcinoid heart disease, systematic literature review, outcomes
The Epidemiological Study of Neuroendocrine Neoplasms: A Single-Center Retrospective Analysis of 710 Patients in China

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Introduction: China hasn’t established a national database of NENs yet, thus, this epidemiological report is based on a single-center retrospective analysis. Aim(s): To review NEN pts in our center, with respect to epidemiology, pathology and clinical diagnosis of tumor. Materials and methods: This was a retrospective analysis of 710 pts with NENs (except SCLC), at China-Japan Friendship Hospital, from Jan 2012 to Sept 2016. Clinical and pathological information were collected. Results: Of the 710 pts, the gender ratio (male to female) was 1.08, and the overall mean age of 51.5 years. The tumors were primarily located in the digestive system (561 cases, 79.0%), thorax (including lung, thymus and mediastinum, 56 cases, 7.9%), and other sites (56 cases, 7.9%); and 37 cases were unknown primary (5.2%). Among 561 digestive NENs, the primary sites covered stomach (177 cases, 31.6%), pancreas (172 cases, 30.7%), rectum (136 cases, 24.2%), duodenum (31 cases, 5.5%), jejunum and ileum (17 cases, 3.0%), appendix (11 cases, 2.0%) and other sites (17 cases, 3.0%). Upon diagnosis, most pts were at stage I (187 cases, 26.3%) and stage IV (294 cases, 41.4%). Pathologically, the tumor grading was G1 in 294 (41.4%) cases, G2 in 229 (32.3%) cases, and G3 in 153 (21.5%) cases, and 34 (4.8%) cases cannot be classified. Conclusion: This single-center study indicated that the most common primary site of NENs was digestive system. Different from the American or European reports, the incidence of small intestinal NENs was low in this study, and carcinoid syndrome was rare. Keywords: nen, epidemiology
National Cancer Intelligence Network Data for NET in England - Accuracy by Comparison to a Large Clinical Database


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Introduction: Data on all cancers is collected centrally for England using ICD-O-3 coding and it is entered into the National Cancer Intelligence Network (NCIN) database. Every pathology report is collected together with laboratory, radiology, admission episodes, clinic review, survival together with demographics. Aim(s): The NCIN database was used to extract data on NET for England for the years of 2013/2014, to assess survival and to validate the data by comparing to a large clinical database. Materials and methods: Data on pathological morphology together with site of disease were extracted from an agreed code list for 2013-14 which are the first years to use the OCD-O-3 coding. Data on one-year survival and stage was extracted. A clinical database from was used to extract patients diagnosed for the same years of interest and this was then linked to the NCIN data. Results: 16,634 NET were diagnosed in 2013-14 and 50% were excluded as small cell lung cancers (sclc). Population incidence rate was 7 per 100,000 persons excluding sclc. 50% were male. No clear geographical or racial variations. One year survival of "carcinoid" was >80%. Out of 327 pts from a clinical database diagnosed during 2013/14, 32 were missing and 27 misclassified in NCIN. Of the 32 missing, 10 were diagnosed outside UK or were outside the NHS. Of the 22 remaining, 3 were appendix, 4 ileal, 14 pancreatic, one unknown. Conclusion: The NCIN data for England contains 93% of NHS clinical cases and provides powerful data for future analysis. Keywords: registry, incidence, mortality
Neuroendocrine Neoplasm Registry: Single-Centre Experience and Outcomes

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Introduction: Neuroendocrine neoplasm (NEN) registries are highly needed to investigate epidemiology of NEN, collect and deliver data on efficacy of management strategies in NEN and improve quality of NEN pts care. Aim(s): To present outcomes of tertiary referral centre NEN registry. Materials and methods: NEN pts referred to Department of Endocrinology, Medical University of Silesia, Katowice, between 2005 and 2015, were included in the registry. Clinical data of the pts were deposited in the registry. Results: Data on 688 NEN pts were available. Pts median age at diagnosis was 63 yrs (21-90); 61% were females. NEN comprised GEP-NEN (gastroenteropancreatic NEN): 79% and non-GEP-NEN: 21% inc. lung NEN. GEP-NET comprised p-NET 21%; colorectal NET 15%; Si-NET 11%; appendiceal NET 3.5%; NET of unknown primary (most probable GEP origin) 14%. At diagnosis 37% pts were symptomatic with abdominal pain in 12.4%, diarrhoea 11.4%, flushing 0.1%. 514 NEN were non-functioning, 133-functioning. 47% NEN were G1; 21% G2; 9% G3. During pts journey regional lymph node involvement developed in 31%pts, distant metastases in 56%. At diagnosis CgA and 24-hr urine 5-HIAA were raised in 40% (out of 601pts), 17% (out of 597pts), respectively. Surgery was performed in 57% pts, SSA administered in 28%, chemotherapy 14%, PRRT 7.4%. Conclusion: Presented registry deposits extensive data on our NEN pts. Continuation of the registry is warranted. Multinational cooperation in joining national registries records is highly needed. Keywords: nen, single centre registry
Comparative Analysis of Computed Tomography Features in Pancreatic Neuroendocrine Neoplasms (pNENs) with Different Pathological Grade (G1 and G2)

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Introduction: Computed tomography (CT) is the most commonly used preoperative tool for pNENs. Aim(s): To analyze the preoperative computed tomography (CT) features between G1 and G2 pancreatic neuroendocrine neoplasms (pNENs) and explore the diagnostic ability of distinguishing G1 from G2 pNENs. Materials and methods: 56 pNENs who received preoperative enhancement CT between January 2010 to November 2015 in Shanghai Changzheng Hospital and Changhai Hospital were recruited in this retrospective study. CT images of all pNENs were reviewed. Differences in clinic pathologic features and CT features between G1 and G2 pNENs were compared. ROC analysis was performed to explore the significance of relative and absolute CT value in the diagnosis of pNENs G1 and G2. Results: Both absolute and relative CT value at arterial phase, portal phase and absolute CT value at delayed phase were significantly higher in G2 pNENs than in G1 (P<0.01). Moreover, ROC analysis demonstrated that absolute and relative CT value at arterial phase, portal phase and absolute CT value at delayed phase could differentiate efficiently G1 pNENs from G2 pNENs. Conclusion: CT characteristics were different between G1 and G2 pNENs. Absolute and relative CT value at arterial phase, portal phase and absolute CT value at delayed phase could be used for preoperative assessment of G1 and G2 pNENs. Keywords: ct pnens
Comparative Analysis of CT Features in pNENs with Different Pathological Grade (G1 and G2)

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Introduction: Computed tomography (CT) is the most commonly used preoperative tool for Pancreatic Neuroendocrine Neoplasms (pNENs) Aim(s): To analyze the preoperative computed tomography (CT) features between G1 and G2 pancreatic neuroendocrine neoplasms (pNENs) and explore the diagnostic ability of distinguishing G1 from G2 pNENs. Materials and methods: 56 pNENs who received preoperative enhancement CT between January 2010 to November 2015 in Shanghai Changzheng Hospital and Changhai Hospital were recruited in this retrospective study. CT images of all pNENs were reviewed. Differences in clinic pathologic features and CT features between G1 and G2 pNENs were compared. ROC analysis was performed to explore the significance of relative and absolute CT value in the diagnosis of pNENs G1 and G2. Results: Both absolute and relative CT value at arterial phase, portal phase and absolute CT value at delayed phase were significantly higher in G2 pNENs than in G1 (P<0.01). Moreover, ROC analysis demonstrated that absolute and relative CT value at arterial phase, portal phase and absolute CT value at delayed phase could differentiate efficiently G1 patients from G2 patients. Conclusion: CT characteristics were different between G1 and G2 pNENs. Absolute and relative CT value at arterial phase, portal phase and absolute CT value at delayed phase could be used for preoperative assessment of G1 and G2 pNENs. Keywords: ct pnens
Prospective Observational Study 1 on the Prognosis of Patients with Unresectable Advanced Gastrointestinal and Pancreatic Neuroendocrine Tumors (PROP-UP 1 Study) in Japan

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Introduction: No previous observational studies on the prognosis of advanced gastroenteropancreatic neuroendocrine neoplasms (GEP-NENs) [pancreatic neuroendocrine neoplasms (PNENs) and gastrointestinal neuroendocrine neoplasms (GI-NENs)] exist in Japan. Aim(s): We planned a retrospective and prospective observational study on the prognosis of patients with unresectable advanced GEP-NENs (PROP-UP 1 and 2). PROP-UP 1 is a retrospective multicenter study to estimate a cut-off value of Ki-67 index between G1 and G2. PROP-UP 2 is a prospective study to verify the results of PROP-UP 1. In this paper we analyzed the characteristics of patients registered to PROP-Up

Materials and methods: PROP-UP 1 included individuals diagnosed with advanced (unresectable or recurrent after curative resection) GEP-NENs from January 2012 up to IRB approval. The primary endpoint is overall survival from diagnosis to last follow-up or death. The main secondary endpoint is to assess a cut-off value of Ki-67 index between G1 and G2. Results: 182 patients with GEP-NEN were enrolled in PROP-UP 1. PNEN accounted for 61.0% and GI-NEN for 35.2%. Frequencies of NETG1/G2/NEC/MANEC among all PNENs were 12.6/52.3/30.6/1.8%, respectively. Frequencies of NETG1/G2/NEC/MANEC among all GI-NENs were 14.1/26.6/50.0/9.4%, respectively. Conclusion: We reported the characteristics of patients registered to PROP-UP 1. The results from PROP-UP study will hold promise to clinical practice in advances of the field of GEP-NENs. Industry sponsored.

Keywords: prop-up, japan, gep-nen
Changes in the Frequency and Epidemiology of the Gastroenteropancreatic Neuroendocrine Tumors, Diagnosed in the University Hospital of Pleven, Bulgaria from the Period 2010 to November 2016

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Introduction: During the recent years there has been an observed tendency of increased frequency of gastroenteropancreatic neuroendocrine tumors (GEP-NETs) all around the world due to the clinicians' improved knowledge about the diagnostic and treatment of these tumors. We have discovered a correlation between world tendency and the local tendency we have observed in the University Hospital of Pleven, Bulgaria from 2010 to November 2016.

Aim(s): The aim of our study is to check the validity of this tendency and the hypothesis that the popularization of NETs and the creation of specialized centers for these tumors leads to the increase of their frequency.

Materials and methods: This is a retrospective population based study about GEP-NETs using data from Regional Cancer Registry of Pleven for the observed period. It includes epidemiological information and data about the pathohistological characteristics.

Results: There are 49 cases of GEP-NETs registrated for the observed period. For 2010 – 2(4.08%) cases, 2011 – 3(6.12%), 2012 – 4(8.16%), 2013 – 8(16.33%), 2014 – 9(18.37%), 2015 – 11(22.45), 2016 – 12(24.49%).

Conclusion: The frequency of GEP-NETs registrated in our study has increased from 4.08% to 24.49% for the observed period and this corresponds to the world tendency. Because there are no pathognomonic symptoms for their recognition it's best for their timely diagnostic to improve the clinicians' knowledge about them by creating centers of excellence for NETs.

Keywords: gep-nets, epidemiology, centers of excellence
Pancreatic Neuroendocrine Tumors (pNETs): A Population-Based Analysis of Epidemiology and Outcomes

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Introduction: pNETs are rare and outcomes vary by stage, grade and presentation. The incidence and stage at diagnosis is changing. Aim(s): To analyze changes in epidemiology and prognosis of patients (pts) with pNETs in a recent period. Materials and methods: Pts diagnosed with pNETs from 2000 to 2013 were identified in the SEER Registry. Overall survival (OS) was analyzed with the Kaplan–Meier method. Prognostic variables were studied with Cox proportional hazards models. Results: 5993 pts with pNETs were studied. An increase in annual incidence from 0.3 to 1.2/100.000 was seen, largely explained by an increase in number of pts with localized pNETs at diagnosis. The OS for the entire cohort was 54 months (95%;CI 50-58) and 5-year OS in localized, locally advanced and metastatic disease was 81.7%, 62% and 26%. OS was better for pts diagnosed after 2008 (HR 0.73; 95%CI, 0.69-0.79; P<0.0001) and this remained significant after excluding pts with localized disease (HR 0.85; 95%CI, 0.78-0.92; P=0.0002). Factors favorably associated with OS included younger age, female sex, early stage, low grade, and surgery. In metastatic disease, pts who had surgery had better OS (HR 0.36; 95% CI, 0.3-0.45). Conclusion: The incidence of pNETs is rising with more pts being diagnosed at earlier stage. The OS has improved over time, likely due to stage migration and more active therapy. Younger age, female sex, lower grade and stage are associated with better survival. Surgery predicts better survival, even in presence of metastatic disease. Keywords: pancreatic nets, survival
Neuroendocrine Neoplasm Trends over 32 Years in Queensland, Australia

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Introduction: Incidence of Neuroendocrine neoplasms (NENs) has been increasing worldwide. Aim(s): This retrospective population-based analysis describes demographics, incidence and mortality of NENs across Queensland. Materials and methods: Patients diagnosed with NENs were obtained from the Queensland Oncology Repository. Findings include the overall and site-specific incidence, mortality and cause specific survival. Results: 3,696 NENs were diagnosed between 1982 and 2014. The median age was 60 years and 49\% were males. Almost one third (35\%) resided in rural areas. The incidence of NENs increased by 79\% from 1.4 cases to 6.7 cases per 100,000 over the 32 year period. Despite the increase in incidence, mortality rates have remained low, from 0.3 cases in 1982 to 0.5 cases per 100,000 in 2014. NENs were most commonly diagnosed in the lung (23\%), small intestine (23\%) and rectum (18\%), comprising of 64\% of all cases. However, over the last 5 years NENs diagnosed in the small intestine have risen to become the most common site. Cause specific 5yr survival from 1995 – 1999 was 79.4\% (95\% [CI 75.3, 83.5]) and improved to 93.4\% (95\% [CI 91.5, 95.4]) in the years 2010 – 2014. Over 50\% of patients are still living 20 years after diagnosis. Survival also varies on primary site, the highest being for rectum and poorest in pancreas. Conclusion: The incidence of NENs in Queensland is rising and there is variation in primary site distribution. Survival from NENs is improving, consistent with studies worldwide. Keywords: incidence, mortality, survival, australia
Introduction: GEJ-NEN is mostly poorly differentiated NEC with poor prognosis. **Aim(s):** This study was to analyze the clinicopathological features and prognostic factors of Chinese patients with GEJ-NEN. **Materials and methods:** The clinicopathological data of 205 patients with GEJ-NEN from 9 centers were retrospectively analyzed. **Results:** 205 patients were enrolled from September 1999 to January 2016. The ratio of male to female was 5.8:1.0, the median age was 62 years (35-85), and the maximal tumor diameter was 4.5±1.8 cm. 6 (2.9%) cases were functional. 3 (1.5%) cases were NET, 158 (77.1%) were NEC and 44 (21.4%) were MANEC. The median Ki67 index was 70%. The case of TNM stage I, II, III and IV was 1 (0.5%), 27 (13.2%), 96 (46.8%) and 37 (18%), with 44 (21.5%) unknown. At diagnosis, 113 (55.1%) had regional lymph node metastases and 37 (18%) had distant metastases. 155 (75.6%) cases received surgery. Until September 2016, the follow-up rate was 81.0% (166/205). 81 patients died, with a median survival time 26.9 months (95%CI 19.25-34.49). The 1, 3, 5-year overall survival rate was 73.6%, 38.3% and 24.8%. Regional lymph node metastasis, distant metastasis and clinical stage were prognostic factors. The Ki67 index did not impact on survival, and the survival of MANEC seemed longer than that of NEC, but need further analysis. **Conclusion:** The majority of the cohort is male and nonfunctional, with large size tumor. At diagnosis, most patients had regional lymph node metastasis and distant metastasis, which were the prognostic factors. **Keywords:** gastroesophageal junction, neuroendocrine neoplasm
(E1)
Prognostic Factors That Mandate Long Term Follow Up Following Surgery for Appendiceal Neuroendocrine Tumours (aNETs)

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Introduction: Appendiceal neuroendocrine tumours (aNETs) are usually diagnosed incidentally at appendicectomy and rarely recur. Current ENET guidelines inform their management and highlight areas of uncertainty. Aim(s): To identify risk factors that predict lymph node (LN) metastasis, residual disease at completion surgery, or disease recurrence, and, assess survival by ENET stage. Materials and methods: Retrospective analysis of 93 patients diagnosed with aNETs between 1990 and 2016, using our centre’s prospective NET database. We assessed risk factors for nodal metastasis, for residual disease at completion surgery, or recurrence using logistic regression models, and, survival using Kaplan-Meier analysis. Results: LN metastasis were significantly (p= 0.0015) predicted by tumour size >2.0 cm, residual disease by tumour grade ≥G2 (p= 0.0418) and GCC histology (p= 0.0390), and, recurrent disease by GCC histology (p= 0.0002). The only case of recurrence where aNET was non-GCC involved R1 resection of ENET stage 3a primary 16.5 years prior. Respective disease-specific 5 year survival for ENET stages 1, 2a, 2b, 3a, 3b and 4 were 100%, 100%, 93%, 100%, 71%, and 67%, being significantly worse in ENET stages 3b and 4 (p≤0.016).

Conclusion: Tumour size >2.0 cm remains a predictor of LN metastasis. GCC histology not only predicts recurrence, but, also predicts residual disease alongside grade ≥G2. Poor survival of patients with advanced ENET stage 3b and 4 disease; with GCC histology or with R1 resection mandates extended follow-up. Keywords: appendix net
(E2)

Dedifferentiation of Metastatic Pancreatic Neuroendocrine Neoplasms

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Introduction: Neuroendocrine neoplasms (NENs) exhibit significant differences in growth behavior. Their metastatic disease may dedifferentiate presenting a more aggressive biological behavior. Aim(s): Prevalence of dedifferentiation of metastatic pancreatic NENs (pNENs)

Materials and methods: Dedifferentiation was defined by new biopsy of metastasis and the identification of a higher Ki-67 to increase the grade of differentiation

Results: 6/201(3%) pNENs patients presented dedifferentiation: 58±5 years (3 males), 5(83%) with sporadic pNEN, 1 with MEN1. At presentation, 1 had Stage 3, 5 Stage 4 pNENs; 2 had Ki-67 1%, 5 5%; upon dedifferentiation, 1 had Ki-67 8%, 1 30%, 2 50%, 1 60%, 1 70%. At presentation, 3 patients were managed by surgical approach. As 1st line treatment 2 patients received somatostatin analogs (SAs) monotherapy, 2 SAs plus everolimus, 1 SSAs plus everolimus plus peptide receptor radionuclide therapy, 1 followed-up without treatment. At differentiation, all patients had metastases: 4 liver, 1 liver along with bone, 1 liver with ovaries and breast metastases; all had positive Octreoscan; 2 had functional syndrome (1 carcinoid syndrome, 1 insulinoma). Progression free-survival (PFS) for 1st line treatment was 36±43 months, while PFS of further therapies varied from 23±25 to 7±8 months (8 lines of treatment registered). At the last follow-up, 2(33%) patients were alive with overall survival 328±541 months

Conclusion: The dedifferentiation of NENs implies a more aggressive biological behaviour and worse overall survival

Keywords: dedifferentiation
(E3)
Prognosis and Treatment Outcomes of Patients with Mixed Adenoneuroendocrine Carcinoma (MANEC) – A Single Cancer Center Experience

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Introduction: Mixed adenoneuroendocrine carcinomas (MANEC) are rare tumors, commonly treated in analogy to adenocarcinomas (AC) or neuroendocrine carcinomas (NEC) without systematic data regarding the optimal treatment strategy. Aim(s): To analyze the treatment outcomes of MANEC patients. Materials and methods: Updated retrospective analysis of all patients with MANEC at our center between 10/2001 and 09/2016. Results: In the 58 patients identified, overall survival (OS) from diagnosis was 32.8 months. 35 patients in a localized stage underwent surgery, median recurrence-free survival (RFS) was 12.9 months. In multimodally treated patients (including chemotherapy and/or radiotherapy) vs. patients receiving surgery alone RFS and OS were significantly prolonged with 14.9 vs. 7.0 months (p=0.0071) and 75.0 vs. 18.0 months (p=0.0041) respectively. 25 patients received palliative first-line chemotherapy for metastatic disease. Partial response (PR) was observed in 48.0 % and stable disease (SD) in 20.0 % of cases. Median progression-free survival (PFS) and OS was 5.2 and 16.3 months respectively without any significant difference between NEC and AC regimens. 12 patients received a second-line therapy with SD in only 1 patient as best response. Conclusion: In this largest reported MANEC cohort so far, prognosis of localized MANEC is improved by multimodal treatment. In first-line therapy for metastatic MANEC, both regimens for AC and NEC seem equally effective. Second-line therapy has only limited benefit. Keywords: manec, mixed adenoneuroendocrine carcinoma

Neuroendocrinology 2017;105(suppl 1): 1-338
High Rate of Second Neoplasms in Patients with a Bronchial Neuroendocrine Tumor

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Introduction: Bronchial neuroendocrine tumors (NETs) are classified as typical carcinoids (TC), atypical carcinoids (AC), large cell neuroendocrine carcinomas (LCNEC), or small cell lung carcinomas (SCLC). Aim(s): We retrospectively reviewed the management, long-term follow-up and clinical outcome of bronchial NETs at our institution. Materials and methods: All patients diagnosed with TC, AC, or LCNEC at our institution from 1995 to 2015 have been included. Patients with SCLC were excluded. Clinical, diagnostic, therapeutic and follow-up data have been collected and analyzed. Results: Forty-seven patients were included in the study (24 males, mean age 55 years). Thirty-seven had TC, five AC, one LCNEC. In four cases the histology was inadequate for more precise characterization. Forty-four patients underwent surgery. Five patients developed metastatic disease. Eight patients died, four of them as a consequence of the progression of the disease. A systematic plan of management and follow-up of bronchial NETs was not in place at our institution during the study period. Fourteen patients have been diagnosed with one or more second neoplasms (lung squamous cell cancer, colorectal cancer and renal cancer being the most common diagnoses). Conclusion: The clinical outcome has been satisfactory in most patients though a systematic management and follow-up plan was not in place. A high rate of second neoplasms were observed, suggesting that a careful follow-up should be recommended in patients with a bronchial NET. Keywords: bronchial net, carcinoid, lung, epidemiology
Patterns of Treatment and Prognosis of Gastroenteropancreatic Neuroendocrine Neoplasms (GEP-NENs): Results from Multicenter Database of China

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Introduction: The multicenter studies of large-volume database about gastroenteropancreatic neuroendocrine neoplasms (GEP-NENs) patients is rare in China. Aim(s): To analyze the current status of GEP-NENs in the southern of China. Materials and methods: From 2005 to 2015, a total of 1183 patients with complete clinicopathological data, treatment types and survival information were retrospectively collected from a multicenter database. Results: The most common primary site of occurrence was the rectum (37.4%), pancreas (28.1%), stomach (20.7%), small intestine (7.2%), appendix (3.4%) and colon (3.3%). The 5-year survival rate of G1, G2 and G3 tumors were 90.9%, 71.2%, and 33.0% (P<0.001). The 5-year survival rate of patients with stage I, II, III, and IV tumors were 94.0%, 84.9%, 56.0% and 34.6% (P<0.001). Of note, our data have shown that patients with distant metastasis who had palliative surgical treatment had a better prognosis than those without surgery (P=0.003). Similar survival benefits were also found in both NET (P=0.031) and NEC (P=0.046) patients. In multivariate analysis, age, G classification, lymph node metastasis, distant metastasis, and surgical treatment were found to be independent prognostic factors. Conclusion: This is the first multicenter study providing clinicopathological information, pattern of treatment and outcomes in Chinese GEP-NENs patients. Our data have shown that palliative surgical treatment can improve the prognosis of stage IV GEP-NENs patients. Keywords: gastroenteropancreatic neuroendocrine neoplasms, treatment, prognosis, china
Natural History of Type 1 Gastric Carcinoid (gNENs) and Risk of Adenoma/Adenocarcinoma in Endoscopic Surveillance Programme

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Introduction: Patients with gNENs & autoimmune gastritis are exposed to 2 malignant risks: 1) transformation of gNENs, felt to be low & guidelines advocate either resection of all lesions or selective endoscopic mucosal resection (EMR) of larger lesions; 2) ill-defined risk of gastric adenoma/adenocarcinoma.

Aim(s): The aim is to assess the adequacy of surveillance in detecting disease progression.

Materials and methods: Retrospective analysis of patients with type 1 gNENs (2005 to 2016) where selective EMR used for gNENs ≥10mm & carefully appraised for adenocarcinoma. Disease progression defined as gNENs requiring EMR or surgery.

Results: Of the 54 patients included, 67% were females with a median age of 59 (IQR 47-70) years. 4 patients (7%) had adenoma (1) or adenocarcinoma (3) on index or surveillance. Metastatic disease from gNENs was seen in 3 patients (6%): liver (1) or nodal (2). 36 patients underwent surveillance for a median of 54 (9-143) months. When followed for 10 years, 28% with gNENs had disease progression requiring EMR. At surveillance, 1 patient developed adenocarcinoma (pT1sm) & another with low-grade adenoma (EMR). There were no significant differences in Ki-67 [2(2-6) vs 2 (2-3)]% or serum gastrin [1058 (318-1810) vs 1191 (842-2075)] mU/L in patients requiring EMR compared to patients without.

Conclusion: Close to a third of patients undergoing surveillance for type 1 gNENs required EMR when followed for 10 years. Surveillance appears adequate in detecting progression but a higher than expected risk of adenoma/adenocarcinoma was observed.

Keywords: type 1 g-nens
(E7) - SELECTED FOR POSTER WALKS
Enhanced Prognostication of Grade 1 Small Bowel Neuroendocrine Tumours with Multi-Parametric Clinicopathological Assessment

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Introduction: Most small bowel neuroendocrine tumours (SBNET) are Grade 1 (G1), and exhibit at least nodal metastasis at diagnosis. The clinical behaviours of G1 SBNET remain poorly predictable. The ‘NET nomogram’ developed by Modlin et al. designates SBNET as low/medium/high risk by mathematical analysis of 15 clinicopathological parameters. Aim(s): To compare the prognostic power of staging and the NET nomogram in G1 SBNET. Materials and methods: Retrospective case review of 62 surgical G1 SBNET patients from 2 tertiary centres. Tumours were categorized low/medium/high risk based on nomogram scores. Survival analyses utilised Kaplan-Meier. Results: Cohort: females 42%, median age 57.5yrs. Staging: 7 I-IIA, 17 IIIB, and 38 IV. Median follow up: 61.5months (range 2-242) with 17 deaths. Stage was not associated with survival (p=0.332). Nomogram risk groups: 40 low (64.5%), 12 medium (19.4%) and 10 high risk (16.1%). Median survivals: low 156mo, medium 129mo and high risk 62mo (p=0.005). Similar results were obtained in IIIB/IV tumours (171, 143 and 126mo, respectively; p=0.006) and in stage IV tumours (114, 129 and 62mo, respectively; p=0.035) Conclusion: Most SBNET are G1, thereby limiting the predictive abilities of single-parameter systems. Multi-parameter analysis with mathematical algorithms, e.g. the NET nomogram may be informative in predicting tumour behaviour and outcome in ostensibly homogeneous sets of SBNET. Addition of molecular parameters is likely to further increase the accuracy of prognostication. Keywords: nomogram, stage, grade

Neuroendocrinology 2017;105(suppl 1): 1-338
Prevalence of Carcinoid Heart Disease in Patients with Disseminated Small Intestinal NET

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Introduction: In patients with small intestinal neuroendocrine tumours (SI-NETs), serotonin may induce fibrosis and lead to carcinoid heart disease (CHD) with right sided valvular dysfunction. Aim(s): Our aim was to investigate the prevalence of CHD in patients with disseminated SI-NET.

Materials and methods: This was a prospective study of patients with disseminated SI-NETs seen at our outpatient clinic between 2014-2016. 53 patients were evaluated with 2D and 3D transthoracic echocardiography. Diagnosis was based on assessment of all four valves, and right ventricular size and function. Valve regurgitation and stenosis was quantified according to European Society of Cardiology guidelines. A validated scoring system was used to characterize each affected valve and calculate a carcinoid score.

Results: Seven patients (13%) had evidence of CHD. All had tricuspid valve involvement with thickening of leaflets and moderate to severe tricuspid insufficiency. Three patients also had involvement of the pulmonary valve. The right ventricle was dilated in 3 cases. All had preserved right ventricular function. No patients had left sided CHD. The median echocardiographic score in those with cardiac involvement was 10, compared to a median of 3 in those without cardiac involvement. Two patients were treated surgically with tricuspid valve replacement. Conclusion: 13% of patients with disseminated SI-NET had CHD, irrespective of symptoms. We recommend screening with echocardiography in all patients with disseminated SI-NET. Keywords: carcinoid heart disease, si-net
(E9) - SELECTED FOR POSTER WALKS

Typical Bronchial Neuroendocrine Tumours with Advanced Disease: A Misleading Biology

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Introduction: Bronchial NETs are graded by histological classification into ‘typical’, ‘atypical’ NETs or small and large neuroendocrine carcinoma’s. Typical NETs are regarded as being low-grade malignant however metastatic disease can still develop. Aim(s): We sought to determine the incidence of metastatic typical bronchial NETs and investigate imaging and treatment used in their management. Materials and methods: We performed a retrospective analysis of all bronchial NETs. From those identified as typical NETs, we analysed clinical records in those who presented with advanced disease (Stage IV) to our unit. Results: From 144 ‘Typical’ NETs, 25(17%) had advanced disease. Median age at diagnosis was 58. 19/25 had liver metastases, 15/25 skeletal metastases, and 15 had carcinoid syndrome (CS). Functional imaging with FDG PET scan was positive in 6/9 patients and somatostatin receptor scintigraphy (SRS) positive in 14/19 and 4/11 demonstrated avidity in both. 18 patients were treated with somatostatin analogues predominantly for CS symptoms. 10 patients treated with peptide radiolabelled receptor targeted therapy with a median Time-To-Progression (TTP) of 27 months. 11 patients received chemotherapy with median TTP of 16 months with 3 patients demonstrating partial response. Conclusion: Typical bronchial NETs can lead to advanced disease in up to 20% of patients. Their behavior can be aggressive and is not predictable by histology alone. Functional imaging with both FDG and SRS may help determine the most appropriate treatment. Keywords: bronchial, typical
(E10)
Improving Outcomes for Patients with Resectable Small Bowel NET Tumours; Five Year Experience from a Tertiary Centre

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Introduction: There remains controversy about which patients benefit from removal of their primary small bowel tumour and whether this should be performed in a specialist tertiary referral hospital as an elective procedure. Aim(s): To elucidate important institution specific data Materials and methods: Retrospective cohort study. Patients were identified from the hospital pathology database having had their primary tumour resected between Jan2011 and Dec2015. Indications for surgery were either symptomatic primary or attempted curative resection. Patients with encased main SMA or SMV were considered unresectable. Results: 100 patients were included, of which 49 had small bowel surgery in the tertiary centre; of these 59% (n=29) had metastases (Stage IV) at the time of surgery. Overall mean survival was 182 months with 5 yr survival 87%. There was no postoperative mortality and 26% morbidity; 10.1% Clavien-Dindo ≥Grade3 within our institution. Median overall survival for patients with Stage IV disease having surgery was 156 months. Multivariate analysis of overall survival suggested age at presentation being the only significant factor (p=0.03) with liver metastasis (p=0.07) and surgery within the tertiary centre (p=0.09) not significant. Conclusion: Small bowel NET surgery in our institution is safe and maybe preferable to surgery in a peripheral hospital. Current indications and acceptance criteria for small bowel surgery yield acceptable surgical morbidity. Keywords: small bowel, neuroendocrine tumors, surgical resection
Mixed Adeno-Neuroendocrine Carcinoma (MANEC) of the Gastrointestinal (GI) Tract: Experience of a European Neuroendocrine Tumour Society (ENETS) Centre of Excellence

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Introduction: Knowledge of MANECs is limited. Aim(s): Outcomes of patients (pts) with GI MANEC were evaluated. Materials and methods: Demographic/clinicopathological/survival data of consecutive pts with MANEC (2010 WHO criteria) were reviewed retrospectively. Results: Twenty-five pts were identified (01/06-10/16); median (med) age: 71yrs (range 36-89), 56% male, ECOG PS 0-1: 48%. Primary tumour location; lower GI: 18(72%), upper: 7(28%). The neuroendocrine (NE) component (predominant histology in 44%) was poorly-differentiated (PD) in 24(96%) [Ki-67≥55%: 60%]. Most frequently expressed IHC markers were synaptophysin (100%), CDX2 (76%), CGA (64%). Of 13(52%) pts with localised disease (LA), 12(92%) had curative surgery (2 had neoadjuvant chemoradiotherapy (CR), 1 adjuvant chemotherapy (CT), 1 peri-operative CT) and 1(8%) had definitive CR; 6(46%) recurred. Sixteen pts (64%) were treated for advanced (adv) disease; 7(44%) platinum-based CT, 1(6%) gemcitabine, 8(50%) best supportive care (BSC). Med follow-up was 8.2mo (95%CI 4.5-16.8). Med OS for entire cohort was 14.6mo (95%CI 8.4–not reached [NR]). Med RFS and OS in pts with LA was 15.7mo (95%CI 5.8–NR) and 33.1mo (95%CI 8.4–NR) respectively. Med PFS in pts with adv disease was 3.5mo (95%CI 2–9.1). On univariable analysis, age<70 and adult comorbidity evaluation index (0 vs ≥1) was prognostic for better OS (both p<0.05) Conclusion: The NE component in MANECs was predominantly PD and CT and BSC were offered to pts with adv disease in equal proportion. Keywords: manec, gastroinstestinal tract, overall survival
Meta-Analysis of Recurrence after Curative Surgery of Pancreatic Neuroendocrine Tumors

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Introduction: Follow-up after curative surgery for pancreatic neuroendocrine tumors (pNET) is designed to detect recurrence, however reliable recurrence rates are difficult to deduct from literature. Without this knowledge, appropriate follow-up regimens and indications for adjuvant treatment remain unclear. Aim(s): To gain insight into recurrence after curative resection of grade 1 or 2 pNET. Materials and methods: Literature search was performed on studies reporting recurrence after complete resection of grade 1 or 2 pNET without distant metastases or hereditary syndromes. Excluded were studies with less than 20 patients, patients with R2 resection or (neo)adjuvant therapy. Results: Curative resection was performed in 853 patients between 1982 and 2013, 121 patients had a recurrence. Mean weighted follow-up was 44.1 months. Pooled recurrence rate was 14%. Sub-analyses showed a pooled recurrence rate of 5% for non-functional tumors, 17% for well-differentiated tumors and 7% for R0-resections. Weighted time to recurrence was 21.7 months. Locoregional recurrence was seen in 5%, distant metastases in 10%. Factors associated with worse disease free survival included: tumor size, tumor grade, lymph node metastases, perineural invasion and R1 resection. Conclusion: With rates of 14%, recurrence of pNET is not rare. More research on predictors is needed to identify patients at risk. With this knowledge follow-up regimens can be customized and the role of adjuvant treatment for selected patients can be investigated. Keywords: pnet, recurrence, meta-analysis
A New Scoring System to Predict Recurrent Disease in Grade 1 and 2 Non-Functional Pancreatic Neuroendocrine Tumors


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Introduction: Surgical resection is the preferred treatment for NF-pNET, however recurrence still occurs frequently after curative surgery, worsening prognosis of patients. Aim(s): To predict recurrence in patients with grade 1 or 2 non-functioning pancreatic neuroendocrine tumors (NF-pNET) after curative resection. Materials and methods: Retrospectively patients with grade 1 or 2 NF-pNET without distant metastases, hereditary syndromes were included. Local or distant tumor recurrence was scored. The recurrence-score was developed to predict recurrence within 5-years after curative resection using independent predictors for recurrence. Results: With a median follow-up of 51 months, 211 patients were included. Thirty-five patients (17%) developed recurrence. The 5- and 10-year disease specific/overall survival was 98%/91% and 84%/68%. Overall 5- and 10-year survival was 91% and 68%. Predictors for recurrence were tumor grade 2, lymph node metastasis and perineural invasion. Discrimination (c-statistic 0.81) and calibration (Hosmer Lemeshow chi-square p=0.258) indicated that the ability of the recurrence-score to identify patients at risk for recurrence is good. Conclusion: The recurrence-score could predict recurrence after curative resection of grade 1 and 2 NF-pNET and may identify high-risk patients. A less extensive follow-up could be proposed for patients with low recurrence-risk. For high-risk patients clinical trials should be initiated to investigate whether adjuvant therapy might be beneficial. Keywords: pnet, recurrence, predictive-model.
The Clinical Pathological Characteristics and Prognostic Factors of Rectal Neuroendocrine Tumors: A Retrospective Analysis Based on Multi Center Data

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Introduction: The pathological characteristics and prognosis factors of rectum neuroendocrine tumor still have a lot of uncertainty. **Aim(s):** To analyze the clinical pathological characteristics and the related factors influencing the prognosis of rectal neuroendocrine neoplasms **Materials and methods:** The clinical and follow—up data of 442 patients with rectal neuroendocrine neoplasms admitted between September 1993 and December 2015 in 5 hospitals were analyzed retrospectively. **Results:** Of the 442 patients, the median age was 50.0 years; Average tumor size was 1.378 cm. NETs<1 cm accounted for 66.1%, 1-2 cm accounted for 17.2% and >2 cm accounted for 16.7%. Stage I, II, III and IV accounted for 73.5%, 8.6%, 7.2%, 10.6%; G1, G2, G3 accounted for 76.5%, 14.7%, 8.8%; The median survival time for all 442 patients was 35 months (range, 1-224 months); the overall 5-year survival rate was 85%; the 5-year survival rates for patients in stage I-IV were 95.3%, 94%, 52%, 36%; the 5-year survival rates for patients with G1-3 were 94.4%, 79.9%, 19% respectively; Univariate analysis showed that G grade, T stage, N stage, M stage, TNM stage, functional, gender, medication, surgical therapy, age, size variables survival difference were significant statistically (P<0.05). Multivariate analysis (Cox regression) revealed that G grade (P=0.001), size (p=0.012) and TNM stage (p=0.008) were the independent factors affecting the prognosis. **Conclusion:** That G grade, tumor size and TNM stage are the independent factors affecting the prognosis. **Keywords:** rectal, neuroendocrine neoplasms, prognosis, grade, size, stage.
Validation and Comparison between Current Prognostication Systems for Pancreatic Neuroendocrine Neoplasms: Single Institution Experience with 176 Patients

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Introduction: Presently, the optimal prognostication system for pancreatic neuroendocrine neoplasms (PNEN) remains unknown. Aim(s): To validate and compare the performance of six prognostication systems- the World Health organisation (WHO) 2010 grading criteria, European Neuroendocrine Tumour Society (ENETS) and American Joint Committee for Cancer (AJCC) staging systems, Memorial Sloan-Kettering Cancer Centre (MSKCC) staging and grading systems as well as the Bilimoria criteria in a cohort of patients with PNENs at a single institution. Materials and methods: A retrospective review of 176 patients with histologically proven PNEN was performed. Results: The 5-year OS for the 176 patients was 69%, and 5-year RFS in 119 patients who underwent curative resection was 78%. Comparison between the 6 prognostication systems demonstrated that the WHO system had the lowest AIC score and was hence the best prognostication system in predicting OS and RFS rates in our cohort of patients. ENETS was superior to AJCC in prognosticating OS rates for PNENs, as there was a statistically significant difference in OS across the different stages when stratified by ENETS, while the use of AJCC was limited to distinguishing between patients in stage I and II vs stage III and IV only. Conclusion: All 6 prognostication systems were useful in the prognostication of PNEN. The WHO grading system was the best prognostication system in predicting both OS in our entire cohort of patients and RFS in the subset of patients who underwent curative resection. Keywords: pnen, prognosis

Neuroendocrinology 2017;105(suppl 1): 1-338
Clinical Characteristics and Treatment Outcome of Advanced G3 Gastroenteropancreatic Neuroendocrine Carcinoma (GEP-NEC)- A Retrospective Analysis

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Introduction: Advanced poorly differentiated GEP-NEC are uncommon neoplasms and treated mainly with platinum-based chemotherapy associated with etoposide. Aim(s): To assess the clinical characteristics and various predicting factors. Materials and methods: 10 patients with advanced GEP-NEC, with ki 76 index above 20% treated in our center in the last 8 years were reviewed. Data about site of the primary tumor, presence of metastasis, alkaline phosphatase (ALKP) value and neutrophil/lymphocytes ratio and survival were collected. Results: The characteristics of the patients were: primary tumor (pancreas 50%, gastrointestinal tract 50 %), 90% had hepatic metastasis and only one patient had a locally advanced tumor, ki 67 index was <55% in 50%. The primary was operated at 20 % patients. Octreotide LAR was associated at 70 % of patients. Three patients developed renal insufficiency during treatment. The overall 2-year survival rate was 30%. The ki 67 index, level of ALKP (cut-off 200), and the neutrophil/lymphocytes ratio (cut-off 2) was found to have an impact on survival (p<0.01). Conclusion: Multiple treatments of metastatic GEP-NECs have been developed over the past 20 years, but there is still a critical need for prospective randomized data to guide clinicians on how to proceed with these various ki-67 indexes, the role of ALKP level and the neutrophil/lymphocyte ratio. All these may have a prognostic role in GEP-NEC. Keywords: gep-nec, chemotherapy, prognostic factors
Carcinoid Heart Disease (CHD): Prognostic Value of 5-HIAA and Impact on Survival – A Systematic Literature Review

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Introduction: CHD is a life threatening complication of carcinoid syndrome. Its exact pathophysiology is uncertain but several studies have identified serotonin as a potential key mediator. The amount of serotonin production can be assessed by the dosage of its metabolite 5-HIAA in urine or plasma.

Aim(s): To summarize the evidence quantifying the risk of CHD development associated to high 5-HIAA levels and the impact of CHD on survival.

Materials and methods: A systematic search of MEDLINE, EMBASE and the Cochrane Library databases was conducted. Articles were screened by two independent reviewers using defined inclusion and exclusion criteria.

Results: Among the 19 studies selected for data extraction, 10 reported higher 5-HIAA levels in patients (pts) with CHD than in pts without. 7 studies reported shorter survival in CHD pts than in pts without. 3 studies which conducted multivariate regression analysis to adjust for confounding factors consistently demonstrated the risk of CHD development and/or progression being statistically significantly higher with increasing levels of 5-HIAA (p-value ≤ 0.012). In the presence of CHD, the risk of death was shown to increase 1.30 (p-value = 0.121) to 3.61 (p-value = 0.001) fold in 3 studies.

Conclusion: There is consistent evidence that 5-HIAA level is an independent predictive factor of CHD development and/or progression, and that CHD is a factor of poor survival prognosis in pts with metastatic NET. Industry sponsored.

Keywords: 5-hiaa, prognosis, carcinoid heart disease, survival
Different Long-Term Oncologic Outcomes after Radical Surgical Resection for Neuroendocrine Carcinoma and Adenocarcinomas of Stomach - A Propensity Score Case-Match Approach

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Introduction: The outcome of the gastric neuroendocrine carcinoma (GNEC) was poor. However, there was few studies analyze the difference of long-term outcomes after radical surgery between GNEC and gastric adenocarcinoma (GAC). Aim(s): To explore the differences of in long-term outcomes between GNEC and GAC. Materials and methods: We analyzed clinic-pathological data, which were derived from 100 GNEC patients and 3089 GAC patients with radical gastrectomy during between January 2006 and December 2013. The differences of long-term outcome between the two groups were analyzed by 1:2 propensity score matching (PSM). Results: The 3-years and 5-year overall survival (OS) in the GNEC group were worse than those of the GAC group, whereas the disease-free survivals (DFS) were similar. Although mean recurrence times were similar, the mean post-recurrence survival (PRS) of the GNEC group was significantly worse (5.2 vs. 14.8 months, p<0.001). There was a strong negative correlation between a high Ki-67 positive index and OS. Cox regression analysis indicated that the Ki-67 positive index was an independent factor influencing PRS. Conclusion: The long-term oncologic outcome of GNEC was worse than GAC, which may be relative to its shorter reduced PRS. High Ki-67 positive index was an independent factor influencing PRS. Keywords: gastric neoplasm, neuroendocrine neoplasm, prognosis, propensity score matching study
Clinicopathological Features and Prognosis of 35 Patients with Gastric Neuroendocrine Carcinomas: A Single-Center Experience

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Introduction: Gastric neuroendocrine carcinoma (G-NEC) is an uncommon and aggressive tumor of the stomach. The research on G-NEC is very limited. Aim(s): We retrospectively analyzed the clinical data of 35 G-NEC patients to investigate its clinicopathological features and prognosis. Materials and methods: The clinical data of 35 G-NEC patients who received surgical treatment in Shanghai Huadong Hospital from Jan 2005 to Apr 2016 was reviewed. The survival curves were drawn. Univariate and multivariate analyses were performed. Results: Among the 35 patients, 26 were male and 9 were female, with a median age of 67.9 years. The median survival time was 21.0 months; the 1-, 3- and 5-year survival rates were 76.5%, 43.9% and 30.1%. There were 27 NEC G3 and 8 mixed adenoneuroendocrine carcinomas but there was no survival difference between the two types. 19 patients (54%) received fluorouracil and platinum based chemotherapy but get no survival benefit. Univariate analysis revealed that sex, lymph node metastasis, distance metastasis, stage, and Ki67 index were associated with survival. Multivariate analysis revealed that sex, lymph node metastasis and Ki67 index (≥60%) were independent prognostic factors. Conclusion: A high Ki67 index (≥60%) could be used as a prognostic marker. Though female has a lower incidence of G-NEC, female G-NEC patients could have a better prognosis. The effect of traditional fluorouracil and platinum based chemotherapy on G-NEC needs further study. Keywords: neuroendocrine tumors, stomach, prognosis, ki67
Long-Term Outcomes and Prognostic Factors of Gastroenteropancreatic Neuroendocrine Neoplasms (GEP-NENs): An Update of a Large National Registry (RGETNE)


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Introduction: RGETNE is a national hospital-based GEP-NENs registry coordinated by the Spanish multidisciplinary scientific society GETNE. 

Aim(s): To analyze long-term outcomes and to identify prognostic factors of overall survival (OS). 

Materials and methods: Data were provided online by participating centers and assessed for internal consistency by automatic checks. In addition, on-site monitoring has been conducted by an external independent expert in NENs. 

Results: 2906 patients were registered from 2001 to 2016. Variables significantly (p<0.001) associated with increased survival were: women vs men (15.8 vs 11 years (y)), ≤60 vs >60 years (17.2 vs 8.1 y), MEN vs non-MEN syndrome (NR vs 12.4 y), functional vs non-functional (16 vs 11.8 y), well vs poor-differentiated (16.9 vs 1.2 y), G1 vs G2 vs G3 (23.2 vs 11.7 vs 1.2 y), stage I-III vs IV (15.8 vs 5.7 y), liver vs lung metastases (5.8 vs 2.4 y). 5-years OS rates by primary tumor site were: appendix 91%, small intestine 83%, stomach 71%, pancreas 70%, rectum 63%, colon 61%, hepatobiliar 54%, and unknown 47%. Multivariate analysis confirmed gender, age, stage, grade, tumor differentiation, primary tumor site and localization of metastasis as independent prognostic factors for OS. 

Conclusion: GEP-NENs are neoplasms of heterogeneous clinical behavior. Multiple factors influence outcome, many of which, as opposed to what is observed for other cancers, are far more determinant than stage. 

Keywords: multivariate, neuroendocrine tumor, prognostic factors, registry, survival, univariate

Neuroendocrinology 2017;105(suppl 1): 1-338
A Gene Expression-Based Nomogram Predicts Progression Free Survival in Small Bowel NETs

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Introduction: Nomograms are predictive tools that help prognosticate. A survival nomogram has been validated for small bowel NETs. A circulating NET specific 51 gene signature – the NETest – has efficacy (~95%) as a predictor of progression free survival (PFS). Aim(s): Evaluate whether including molecular information increases the predictive accuracy of a clinical nomogram for PFS in small bowel NETs. Materials and methods: Small bowel NETs (n=84) median follow-up 22 months. Clinical history including age (median: 65 years), gender (43M), grade (NET G1: 60, NET G2: 24), stage (CS: I-IV), functional status, surgery, CgA and SSA use were used. Blood transcript levels (n=51) measured by QRT-PCR (scaled 0-100%). Outcome was PFS (RECIST). Mann-Whitney, McNemar, Kaplan-Meier and Cox-proportional modeling. Results: Follow-up was 21.5 months (15-27); median PFS (mPFS) was 24 months. Informative clinical parameters for PFS included age (>62 yrs, p=0.03, mPFS 26 vs. 23 months) and grade (p=0.05, mPFS 25 vs. 23). NETest levels (>50%) were significantly associated with mPFS (26 vs. 23 months, p=0.02, accuracy 75%). This was more accurate than age and grade (McNemar: p<0.05). Combining clinical parameters with the NETest resulted in the most effective predictor: mPFS 26 vs 21 months (p=0.008, accuracy 80%). Conclusion: A hybrid nomogram (blood transcript analysis and clinical data) has clinical utility and is accurate for predicting PFS in small bowel NETs. Keywords: nomogram, prognosis, netest, pfs, grade, biomarker
Predictive Factors for Survival in Patients with Pancreatic Neuroendocrine Tumours

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Introduction: Pancreatic neuroendocrine tumours (pNETs) comprise a heterogeneous group of neoplasms with rising incidence. However, prognosticators at diagnosis (Dx) are limited. Aim(s): To assess impact on survival of combined clinical, radiological and biochemical factors at Dx.

Materials and methods: Data from 201 patients with pNETs including duration of presenting symptoms, hormone production, size of primary, hepatic metastases, chromogranin A (CgA), resection of primary and tumour grade at Dx (date of the first histopathological data) were retrospectively analyzed using Cox proportional hazards models. Follow-up was complete. Results: Median survival was 4.6 years and the 5-year survival 44%. There was reduced risk of death (p=0.02) for patients undergoing radical primary resection after adjusting for all other variables with a hazard ratio (HR) of 0.44 and 95% Confidence Interval CI(0.22, 0.88). Hepatic tumour load was a negative prognosticator [p value, HR and 95% CI vary for different tumour burden (<25%, 25-50%, >50%); overall, statistical significance was shown]. There was evidence (p=0.043) of an increased risk of death per unit increase in % of the ki67 [HR 1.05, 95% CI(1.002, 1.1)] after adjusting for all other variables. Primary size, symptoms, hormone production, gender, age and CgA did not appear to alter prognosis.

Conclusion: Ki67 and liver tumour burden were the most important negative prognosticators. Radical resection of the primary appears to improve survival. Prospective studies are required to validate these predictive factors.

Keywords: pancreatic nets, prognosis
Introduction: Nomograms are predictive tools that help prognosticate. A survival nomogram has been validated for small bowel NETs has been adapted for other sites. About 50% of NETs occur in the appendix-colon-rectum. Locations have widely differing outcomes (survival 50-100%). Aim(s): Develop individual clinical-based survival nomograms for NETs of the appendix, cecum, ascending colon (AC), sigmoid and transverse colon (STC) and rectum. Materials and methods: Clinical history including age, gender, grade (NETG1, G2 or NET/NECG3), stage (CSI-IV), tumor size, and secretory status were assessed for appendix (n=99); cecum (n=40); AC (n=16), STC (n=23) and rectum (n=99). Uni- and multivariate analyses identified clinically relevant factors. Cox-proportional modeled hazard ratios to develop scores and generate nomograms. Median OS and accuracy for predicting survival were measured. Results: Appendix: gender, secretion and CSIV accurately (100%) predicted outcome (Chi2=89, p<0.001). Cecum, age>55 yr., size>45mm, CSIV and grade were most accurate (88%, Chi2=23, p<0.001). AC: size>45mm, CS>III and grade were 81% accurate (Chi2=3.8, p=0.05). STC: liver and lymph node involvement, CS>III and grade were 78% accurate (Chi2=6, p<0.02). Rectum: male gender, tumor size>10mm, CS>III and grade were 89% accurate (Chi2=59, p<0.0001). Conclusion: Clinically useful NET nomograms can be formulated for individual tumor sites. Multiple information sets allow for accurate survival prediction. Addition of molecular information will likely amplify accuracy. Keywords: nomogram
Introduction: Pancreatic neuroendocrine carcinomas (NEC) including poorly differentiated (NECG3), mixed type (MANEC) and NETG3 are rare of pancreatic neuroendocrine neoplasms. Aim(s): Retrospective analysis of records to determine natural history and outcomes OS and PFS in this group of NEN. Materials and methods: Review of pancreatic poorly differentiated NEN 51 subjects (15.6%) selected. All patient data sets were review consider OS and PFS for clinical stage (CS) and pathological factors type of the cancer cells and Ki-67. Results: A total of 51 pts were included in this study. A female to male ratio 0.89. There were 4 MANEC (8%), 37 NECG3 (72.5%) and 10 NETG3 (19.5%). Mean age of all subjects 56.5 (53.2-59.8). At the initial diagnosis local disease was noted in 4 subjects (7.8%), regional lymph nodes spread in 12 patients (23.5%) and distant mts noted in 35 pts (68.6%). The median OS and PFS in whole group of subjects 12.0 mo (CI15.3-28.7), PFS 6.0 mo (CI 5-11.7). Female OS 17 mo vs. male 7 mo. Local spread was seen only in 4 subjects (8%), regional spread in 12 (23.5) and others had distant mts 35 (68.6%). Those pts with distant mts had OS 9 mo (CI 8.7-25.3) vs. others 30 mo (CI 22.5-43.6), p>0.05. There was no difference in OS in those with initial liver involvement in those without. OS in those with Ki-67<55% OS 19 mo vs. 11.5 mo in Ki-67>55% n.s. Conclusion: Pancreatic NEC are heterogenous group of cancer including different type NECG3, NETG3, MANEC. OS is unfavourable compare to NETG1/2 GEP-NEN. Keywords: nec of the pancreas, os, ki67, cs
Predictors of Survival in Patients with Small Intestinal Neuroendocrine Tumours (SINETs) Associated with Mesenteric Desmoplasia

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Introduction: SINETs represent 30-50\% of small bowel neoplasms with a rising incidence and can be associated with mesenteric fibrosis (MF)

Aim(s): In a published survival analysis of a large cohort of patients with SINETs from our centre the median survival was 10.7 yrs, but studies evaluating predictors of survival in the subgroup of SINETs with MF are lacking

Materials and methods: Case notes of 147 patients with SINETs/MF treated in our centre from 2001-2013 were reviewed. Data collection included: demographics, tumour characteristics, clinical/biochemical data (measured at diagnosis). Univariate (UVA) and multivariate analysis (MVA) were used to identify predictors of survival

Results: The median overall survival was 6.8 yrs. On UVA age>65, volume of liver metastases>50\%of liver parenchyma, carcinoid heart disease, CgA levels>10x upper limit of normal (ULN) and urine 5-HIAA levels>5xULN were associated with a worse survival. Primary resection (but not bypass surgery) was associated with a better outcome. MVA showed that only age>65 and urine 5-HIAA>10xULN remained statistically significant. Primary resection showed a trend as a favourable prognostic factor, but it did not quite reach the level of statistical significance (CoxHR 0.54, p=0.09)

Conclusion: Age>65 and urine 5-HIAA levels>10xULN at diagnosis were predictive of a worse outcome. Patients with SINET/MF have worse overall survival than SINET without MF. Primary resection showed a trend as a predictor of better survival and this needs further evaluation in adequately powered prospective trials.

Keywords: sinets
The Preoperative Blood Lymphocyte-To-Monocyte Ratio Acts As a Superior Prognostic Factor and Predicts Tumor Metastasis in Gastric Neuroendocrine Neoplasms after Surgery

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Introduction: A low lymphocyte-to-monocyte ratio (LMR) has been reported to be a predictor of poor survival in patients with various cancers but has not been examined in patients with gastric neuroendocrine neoplasms (g-NENs).

Aim(s): The aim of this study is to investigate the prognostic significance of the LMR in g-NENs.

Materials and methods: We enrolled 177 patients who had been diagnosed with g-NENs and undergone radical surgery. A nomogram was adopted to predict recurrence free survival (RFS) and overall survival (OS).

Results: The LMR was lower in patients with g-NENs than in matched normal volunteers (P<0.05). Multivariate analysis demonstrated that the LMR was an independent prognostic factor for RFS and OS. The concordance index (C-index) of the nomograms for RFS (OS), which included the lymph node ratio, histological type and the LMR, was 0.776 (0.760), which was higher than the C-index of the traditional TNM system [0.678 (0.667)]. The recurrence rate was 38.9% (69/177), and the median time to recurrence was 10 months. We noted a significant correlation between the LMR and tumor recurrence, especially liver, peritoneal and lymph node metastases (all P<0.05).

Conclusion: The LMR combined with the lymph node ratio and histological type had a more superior ability to predict clinical outcomes in g-NENs patients than the traditional TNM system. Patients with low LMRs require close surveillance to identify tumor recurrence early.

Keywords: gastric neuroendocrine neoplasms, lymphocyte-to-monocyte ratio, prognosis, tumor recurrence
Introduction: The published evidence on gastric neuroendocrine neoplasms (g-NENs) is often based on small series of patients. Aim(s): The aim of this study is to investigate trends in incidence and survivals for g-NENs. Materials and methods: Patients diagnosed with g-NENs (n=3523) were identified from the Surveillance, Epidemiology and End Results (SEER) database. Patients diagnosed with g-NENs (n=199) in our department were assigned as validation set. A nomogram was adopted to predict disease special survival (DSS) and overall survival (OS). Results: The incidence of g-NENs is increasing over time at a rate higher than any other cancer [annual percentage change = 6.3, 95% confidence interval 5.6–7.0]. The multivariate analysis identified that patient’s age, sex, T stage, M stage, and histological type were the common independent prognostic factors for both DSS and OS (all P<0.05). The concordance index of the nomograms for DSS (OS) in the training set was superior to that of the 7th edition of AJCC staging system [0.899 (0.849) versus 0.864 (0.783)]. Calibration plots of the nomograms showed that the probability of DSS (OS) corresponded to actual observation closely in both training set and validation set. Conclusion: The incidence of g-NENs has been steadily increasing at a high rate over the past four decades. The nomograms based on SEER database had a more superior ability to predict clinical outcomes for g-NENs patients than the traditional TNM staging system. Keywords: gastric neuroendocrine neoplasms, seer, prognosis, nomogram
A Role for Vitamin D in the Gastro-Entero-Pancreatic Neuroendocrine Neoplasms Outcome: Report on a Series from a Single Institute

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Introduction: Vitamin D deficiency is hypothesized to represent a risk factor in several neoplasms. Aim(s): The aim of this study was to determine whether serum 25-hydroxyvitamin D (25-OHvitD) deficiency represents a risk factor for neuroendocrine neoplasms (NENs) and can be associated to overall survival (OS) and progression-free survival (PFS).

Materials and methods: From 2010 to 2015 138 patients with gastro-entero-pancreatic NENs (F=61, median age 63 years) were included in the study. Serum 25-OHvitD levels, measured at baseline, were defined as deficient if <20 ng/ml. In such cases 25-OHvitD supplementation was administered to the patients. The possible associations between 25-OHvitD levels and disease grading, staging, overall OS and PFS were considered. Furthermore, the possible association between 25-OHvitD supplementation and PFS or OS was evaluated by Cox’s proportional hazards regression.

Results: Median 25-OHvitD levels were 12.9 ng/ml (range 2–32); 94 patients (68%) had <20 ng/ml. An inverse correlation was observed between 25-OHvitD levels and OS (p=0.03, r.s.=-0.18) and PFS (p=0.01, r.s.=-0.22). At Cox’s proportional hazards regression, mortality was not related to 25-OHvitD levels, but there was an association between 25-OHvitD supplementation and OS (p <0.002).

Conclusion: Vitamin D deficiency is highly prevalent among NEN patients. 25-OHvitD supplementation potentially plays an important role not only in the correction of 25-OHvitD values, but also for its influence on the clinical outcome.

Keywords: vitamin d deficiency, net
Heterogeneity of Duodenal Neuroendocrine Tumors: A Multi-Centre Experience in Italy

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Introduction: Duodenal neuroendocrine neoplasms (dNENs) are heterogeneous tumors, which could have a highly variable prognosis. Aim(s): The optimal management of these tumors is still far to be clearly understood. Materials and methods: Retrospective analysis of patients with histologically confirmed diagnosis of dNENs managed at two tertiary referral centers in Italy. Results: From 2005-16, 34 patients were managed at two referral Centers in Italy. 25 patients had G1, 7 G2 and 1 G3 dNEN. 13 patients (38%) showed metastases at the diagnosis: 7 at lymph nodes, 4 at the liver, 2 presented both. Further 4 patients developed metachronous metastases. The dNEN was single in 27 and multiple in 7 patients. Location was bulbar in the majority (11), peri-ampullary in 7 and in the second duodenum in 8. The median diameter was 15 mm. 4 patients had a MEN-1 syndrome. 10 patients had a functioning dNEN (7 gastrinomas and 3 somatostatinomas), of which 8 had metastatic disease. 15 patients (44%) had the dNEN surgically resected, 7 (20%) underwent endoscopic treatment and 9 metastatic patients received both medical therapy and surgery or endoscopy. 6 patients underwent liver-directed therapy. Median OS was 96 months. Over a median follow up of 51 months 10 patients died, 6 of disease-related causes Conclusion: dNENs may be metastatic in up to 50% of cases. Functioning NENs express a high metastatic potential. Nuclear imaging should always be performed. Endoscopy and surgery play a primary role in the disease management. Dedicated guidelines are needed. Keywords: dnenS
(E30)
Effects of Low-Doses Aspirin on Clinical Outcome and Disease Progression in Patients with Gastro-Entero-Pancreatic Neuroendocrine Tumors: Results of a Multicentric Retrospective Study

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Introduction: The chemopreventive effect of aspirin (ASA) has been observed in the setting of colorectal cancer. The impact of aspirin use on clinical outcome of patients with gastro-entero-pancreatic neuroendocrine neoplasms (GEP NEN) has not been evaluated yet. Aim(s): To retrospectively evaluate the clinical outcome of GEP NEN patients treated with ASA. Methods: All the GEP NENs patients followed up in three European Centres, from January 2005 to September 2016, were retrospectively enrolled. The possible association between ASA and disease grading, staging, primary site, overall OS and PFS were evaluated. Results: 253 patients were included (121 M, median age 64 yrs). The site of primary tumor was: stomach in 35, pancreas in 82 (pNEN), the small bowel in 83 (sbNEN), appendix in 27, colon in 19, unknown in 7. Grading was G1 in 154 patients, G2 in 64, G3 in 7; not available in 28. TNM staging was I in 99 patients, II in 16, III in 32 and IV in 86; not available in 10. No clear impact on OS or PFS was observed in patients taking ASA compared to those not taking it. Interestingly, in pNEN an inverse relation was observed between Ki67 and ASA intake ($r=-0.35$, $p=0.008$). In sbNEN an inverse relation between lymphnodes involvement and ASA intake ($r=-0.3$, $p=0.02$) was observed. As expected, ASA intake was related with patients’ older age. Conclusion: Even if ASA therapy seems not to have a direct clinical impact on OS or PFS in NENs, it is associated with lower Ki-67 values and less nodal involvement. Further studies are needed. Keywords: nen, asa
Type 3 Gastric Neuroendocrine Neoplasms: Relationship Between Tumor Size, Ki67 and Clinical Outcome

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Introduction: Sporadic type 3 gNENs are usually malignant with high metastatic potential, mostly large, with a high grade histology. However, little is known on the relationship between tumor size, proliferative index Ki67, and clinical outcome. Aim(s): To evaluate the impact of Ki67 and tumor size on clinical outcome in type 3 gNENs. Materials and methods: Multi-center retrospective study. Linear regression and receiver operating curve (ROC) were used to perform the prognostic analysis. Values are expressed as median (range). Results: 22 pts with type 3 gNENs were evaluated. Median age was 58 yr (39-84). Median tumor size was 16.5 mm (2-50). 6 pts (27.3%) had G1 tumors (Ki67 ≤ 2%), 10 pts (45.4%) had G2 tumors (Ki67 3-20%), and 6 pts (27.3%) had G3 tumors (Ki67 > 20%). 12/22 pts (54.4%) had metastatic disease at time of diagnosis, which were distant in 7 of them (31.2%). Tumor size was significantly associated with the presence of metastases (p=0.022). The cut-off value of 15 mm for tumor size was associated with an increased risk of metastatic disease (AUC=0.762, p=0.023). Median follow-up was 12 months (1-140). During this period, 6/22 pts (27.3%) died of disease. Of these, 5 pts had G3 tumors, and median tumor size was 22.5 mm (5-50). Conclusion: Type 3 subgroup includes heterogeneous diseases with different prognosis according with tumor size and Ki67. A better clinical behavior is observed in G1-G2 tumors, with size <15 mm. In these patients, a more conservative management might be proposed. Keywords: gastric neuroendocrine tumors, ki67, tumor size
External Validation of Prognostic Classification Score for Predicting Overall Survival (OS) of Patients (pts) with Advanced Well Differentiated Neuroendocrine Tumour (WDNET). Neuroendocrine European Prognostic Score (NEP Score Working Group)

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Introduction: Absence of relevant prognostic score (PS) in NET Aim(s): To meet a current need for WDNET pts counseling or stratification in clinical trials, building a PS for OS Materials and methods: Data of 515 pts treated at INT (Milan ENET Center of Excellence) from 1986 to 2012, were used (Training Set, TS). Prognostic covariates were selected in a multivariable Cox model; the final model included patients' age at metastasis, gender, site of primary tumor, metastasis site, time to metastasis, grading, functional status, and primary tumor resection; a 3-classes score was derived by classifying pts based to predicted 10-year OS: 1) ≥70%; 2) ≥30% and <70%; 3) <30%. External validation was performed applying the score to 2 independent sets: population-based data of the RARECARE-net project (validation set 1, VS1, 457 pts) and pancreatic WDNETs cohort (VS2, 415 pts) of Italian multicenter group. The score was evaluated by examining calibration and discrimination (Harrell C index). Results: In the TS 10-year OS in the 3 classes was 0.75, 0.57 and 0.19, with a worsening in VS1 (0.39, 0.26 and 0.05), and improvement in VS2 (1.00, 0.59 and 0.38). Calibration analysis showed that the score systematically overestimated VS1 observed OS (population-based data and not only expert centers) and underestimated VS2 OS (pts treated from 1999 to 2016 with target therapies). The C statistic was 0.662, 0.626 and 0.601 in TS, VS1, and VS2, respectively. Conclusion: Calibration may be required to apply the score to different settings Keywords: neuroendocrine, prognostic score
Heterogeneity of Type 1 Gastric Neuroendocrine Neoplasms

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Introduction: Type 1 gastric Neuroendocrine Neoplasms (gNENs) are defined when atrophic body gastritis is associated. They are mostly multiple, small, with a low grade histology with low metastatic risk. Data on factors associated with malignant tumor behavior in these patients are scarce. Aim(s): Identify subgroups of patients with potential risk of malignant behavior among type 1 gNENs. Materials and methods: Multi-center retrospective study including type 1 gNENs. Tumors were divided according ENETS staging and grading system. Pearson coefficient was used to assess correlation. Results: 117 pts were evaluated, 86 F (73.5%). Median age was 57 yr (27-83). 72 pts (61.5%) had single tumor, 45 pts (38.5%) had multiple tumors. Overall, 140 gNEN lesions were analyzed. Median tumor size was 4 mm (0.5 – 40). 16/140 tumors (11.4%) measured > 1 cm. 109/140 (77.9%) tumors were included in the G1 group, the remaining 31 (22.1%) were G2 tumors. Overall, median Ki67 was 2% (1% – 12%). Ki67 was ≥ 5% in 20/140 tumors (14.2%). A significant correlation was observed between tumor size and Ki67 value (p=0.003). Lymph node metastases were reported in 3/31 pts with G2 (9.6%). One single pt (0.8%) died for disease during an overall median follow-up period of 36 months (2 – 216). Conclusion: Type 1 gNENs have an indolent clinical course, with extremely low malignant potential. This group of NENs includes heterogeneous diseases, in terms of grading and staging. However, a relatively low malignant potential is observed also in G2 tumors. Keywords: gastric nen, grading
Subtype Classification and Clinicopathological Features of Gastric Neuroendocrine Neoplasms: An Analysis of 241 Cases

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Introduction: Definition of type 3 gastric NEN in 2012 and 2016 ENETS guidelines is not clear, so Four-type classification has been proposed. Aim(s): To explore classifications of gastric NEN in Chinese population. Materials and methods: A total number of 241 gastric NEN cases were collected, using data from China-Japan Friendship Hospital and The First Affiliated Hospital of Sun Yat-Sen University, Jan 2011-Jun 2016. According to serum gastrin, 24-hour intragastric pH monitoring and pathological grading, pts with gastric NEN were subdivided into 4 types: type 1 (hypergastrinemia and achlorhydria, related to autoimmune chronic atrophic gastritis), type 2 (hypergastrinemia and ZES, related to gastrinoma or MEN-1, type 3 (sporadic disease with normal serum gastrin level). Poorly differentiated gastric NEC and MANEC belong to type 4. The clinicopathological features, treatment and prognosis of all types were summarized. Results: Among these 241 gastric NEN cases, there were 86 (35.7%) in type 1, 7 (2.9%) in type 2, 61 (25.3%) in type 3 and 87 (36.1%) in type 4. Most type 1 pts received endoscopic resection, while type 4 pts were treated with chemo, or surgery plus chemo. The survival rate of all pts was 74.2%, and 98.8%, 100%, 79.3% and 39.2% in types 1, 2, 3 and 4, respectively. Conclusion: Subtype classification of gastric NEN is significant for making therapeutic decisions and prognostic evaluation. Compared to type 1 and type 2, with good prognosis, type 3 gastric NEN have worse prognosis and type 4 pts have the worst one. Keywords: gastric nen, subtype
VHL Genotype Is Associated with Pancreatic Neuroendocrine Tumors (PNETs) Phenotype in Patients with Von Hippel-Lindau Disease (VHLD)

Introduction: 8-20% of patients with VHLD develop PNETs. However, there are no markers for PNETs progression in VHLD patients. The type of mutation in VHL gene is associated with clinical phenotype of VHLD. **Aim(s):** To determine whether VHL mutation characteristics are associated with PNETs phenotype. **Materials and methods:** A prospective study of patients with VHLD and PNETs with follow-up imaging. VHL mutations were characterized using Sanger sequencing of germline DNA. Disease progression [DP] was defined as growth ≥5mm & ≥20%. **Results:** 182 patients (476 PNETs) were followed for 62.2 months (median, range 3-117). VHL gene was sequenced in 154 patients: 75 patients (48.7%) had a missense mutation [MisM], 51 (33.1%)-deletion, 12 (7.8%)-nonsense, one (0.6%)-rearrangement, and 15 (9.7%) had frameshift mutations. Patients requiring an intervention (n=30) had larger lesions compared with others (2.5±1.5 vs. 1.1±0.8 cm, p<0.001, respectively). Patients with MisM had a higher risk for intervention compared with others in univariate (p=0.02) and multivariate analysis, controlling for lesion size and mutation position (Hazard Ratio=2.74, 95% confidence interval 1.04-7.18, p=0.04), and had trend towards a higher risk for lymph node metastases (Log-rank test, p=0.08) but not for DP (p=0.6). However, MisM in exons 2 or 3 vs. exon 1, had trend towards higher risk for DP (p=0.08). **Conclusion:** Characterization of mutations in the VHL gene may assist in identifying VHL patients at high risk for progression and/or intervention of PNETs. Keywords: vhl, mutation, prognosis
Total 68Ga-DOTATATE-Avid Tumor Volume (TV) Predicts Progression-Free Survival (PFS) and Disease-Specific Mortality (DSM) in Patients with Neuroendocrine Tumors (NETs)

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Introduction: Patients with NETs have divergent survival, even when having the same site of primary tumor, tumor stage and grade. 68Ga-DOTATATE PET/CT has emerged as a sensitive imaging modality for detecting NETs.

Aim(s): To determine if 68Ga-DOTATATE PET/CT imaging has any prognostic utility in patients with NETs.

Materials and methods: Patients with NETs (n=184) were enrolled in a prospective study of 68Ga-DOTATATE PET/CT imaging and comprehensive biochemical analysis. 68Ga-DOTATATE TV was measured in all participants. The primary outcome measures were PFS and DSM during a median follow-up time of 18 months (range 4–35).

Results: 68Ga-DOTATATE TV ≥2.9 ml (1st quartile) was associated with disease progression both on univariate (HR 6.3, 95% CI 2.0–20.2, P=0.002) and multivariate analyses (HR 4.8, 95% CI 1.2–18.4, P=0.02). 68Ga-DOTATATE TV ≥43.6 ml (4th quartile) was associated with lower PFS on univariate analysis (P=0.03). DSM was significantly different by 68Ga-DOTATATE TV (301.7±349.3 vs. 54.4±117.7, dead vs. alive, respectively, P<0.001). On univariate analysis, tumor WHO G3 grade, presence of liver, lymph node and/or bone metastases, elevated urinary 5HIAA (>8 mg/24h) and high 68Ga-DOTATATE TV were associated with higher DSM, whereas on multivariate analysis, only high 68Ga-DOTATATE TV was associated with a higher DSM (HR 14.6, 95% CI 2.1–101.7, P=0.007).

Conclusion: For the first time, we show the utility of 68Ga-DOTATATE TV as a predictive tool for PFS and DSM in a large cohort of patients with NETs.

Keywords: pet, 68ga-dotatate, mortality

Neuroendocrinology 2017;105(suppl 1): 1-338
Prevalence of Pancreatic Neuroendocrine Neoplasms with Serotonin Secretion

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Introduction: Pancreatic neuroendocrine neoplasms (pNENs) are rare neoplasms and represent 1-2\% of all pancreatic neoplasms. These tumors can secrete a variety of hormonally active substances producing distinct clinical symptoms, or can be clinically non-functioning. Pancreatic NENs that secrete serotonin are extremely rare, but their prevalence has not been explored adequately. Aim(s): To examine the prevalence of patients with pNENs and serotonin secretion. Materials and methods: From our unit database patients with increased levels of 5HIAA in 24h urine and/or carcinoid syndrome were included. Results: Out of 445 NENs, 161 had pNEN (36.2\%). Out of 161 pNEN 39 (24.5\%) presented with functional syndrome and 5 (3.1\% of pNEN) had high 5HIAA: 4 grade 2 stage IV and 1 grade 1 stage IIb. Three patients with pNEN and 5HIAA had positive serotonin immunostaining in liver biopsies. At diagnosis, 36\% pNEN and no 5HIAA were stage I, 15.7\% stage II, 8.5\% stage III and 38.6\% stage IV; 56 had liver and 5 bone metastases versus 4 and 1 patients with 5HIAA, respectively. Of 161 pNEN, 133 (82.6\%) received 1st line treatment, including those 5 with 5HIAA secretion. Fifty one (31.7\%) of 161 pNEN received 2nd line treatment, including 3 patients with 5HIAA. Out of 5 with 5HIAA secretion, 3 passed away, after a follow-up of 24, 72 and 192 months respectively, versus 18 patients without 5HIAA. Conclusion: We reported data for patients with serotonin-producing pNEN, a rare entity that may be associated with worse prognosis. Keywords: serotonin-producing pnen, 5-hiaa, prognosis
Treatment and Survival of 351 Patients Diagnosed with Merkel Cell Carcinoma in 2 Melanoma and Neuroendocrine Tumor Expert-Centers in the Netherlands

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Introduction: Merkel cell carcinoma (MCC) is a rare and potentially aggressive neuroendocrine carcinoma of the skin. Because of its frequency, adequate data on treatment and survival are lacking. Aim(s): To describe treatment and survival of patients with MCC referred to 2 expert-centers. Materials and methods: Patients with histologically confirmed MCC in 1990-2014 were included. Data on patient, tumor characteristics and treatment were collected. Primary endpoints were relapse-free survival (RFS), overall survival (OS) and disease-specific survival (DSS). Results: We included 351 patients, 153 (44%) males, with a median age of 74 years (range 28-94). Median follow-up time was 28 months (IQR 13-58). Primary tumor size was determined in 210 (60%) patients with a median of 17mm (range 2-135). At the time of diagnosis 112 (32%) patients had lymph node and 10 (3%) patients had distant metastases. Primary excision was performed in 301 (86%) patients and a lymph node dissection in 88 (25%) patients. Post-operative radiotherapy (RTx) followed in 112 (32%) patients. Primary RTx was given to 9 (3%) patients and primary chemotherapy in 6 (2%) patients. The cohorts' 5-year survival rates were 54%, 58% and 75% for RFS, OS and DSS respectively. Male gender was the strongest predictor of a worse survival Conclusion: Primary treatment consisted mainly of surgery with or without postoperative RTx. The high DSS shows a significant part of patients die of other causes instead of MCC. Male gender was the strongest negative predictor for survival. Keywords: merkel cell carcinoma, nec
(E39) - SELECTED FOR POSTER WALKS
Nomogram Individually Predicts the Overall Survival of Patients with Gastroenteropancreatic Neuroendocrine Neoplasms

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Introduction: A few previous studies have shown that nomograms can predict the survival rates of patients with neuroendocrine neoplasms (NENs). Aim(s): To establish a novel nomogram to predict the overall survival of individual Chinese patients with gastroenteropancreatic NENs (GEP-NENs). Materials and methods: The records of 1,183 patients with GEP-NENs treated at five high-capacity institutions in China between 2005 and 2015 were retrospectively analyzed. In addition, 10,236 GEP-NEN cases from the SEER database were included as external validation set. A multivariate analysis using a Cox proportional hazards (PHs) regression was performed and a nomogram was constructed. Results: The multivariate Cox model identified age, tumor size, G classification, lymph node metastases and distant metastases as independent covariates associated with survival. Regarding the training set, the nomogram exhibited superior discrimination power to that of the 7th AJCC’s TNM classification (Harrell’s concordance index [C-index]: 0.837 vs 0.784, P=0.006). Discrimination was also excellent with regard to the SEER validation set (C-index: 0.808 vs 0.717, P<0.001). The calibration of the nomogram predicted a survival rate that closely corresponded to the actual survival rate. Conclusion: We developed a nomogram that predicted the overall survival rates of patients with GEP-NENs, which suggest a satisfactory clinical utility that might improve individualized assessment predictions of survival risks. Keywords: gastroenteropancreatic neuroendocrine neoplasms, nomogram, prognosis
Multiple Endocrine Neoplasia Type 1 (MEN1): The Experience of a Referral Center in Greece

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Introduction: Multiple endocrine neoplasia type 1 (MEN1) is a genetic disorder involving mainly parathyroid, pituitary and pancreatic neuroendocrine neoplasms (pNENs). Aim(s): The description of staging, grading, primary lesion, presence of functional syndrome, metastatic foci, therapeutic management and outcome of their pNENs.

Materials and methods: 47 patients with MEN1 (26 males; 45(15-67) years) have been observed from 2004 to 2016.

Results: 26(56.5%) patients were the index cases; 27 had positive and 4 negative mutation out of 31, 27(58.6%) had pituitary adenoma (12 functional), 42(91.3%) had hyperparathyroidism, 18 (39.1%) had adrenal adenoma and 1 suffered from adrenal carcinoma. 42(91%) patients had pNENs (12 functional); 1 patient had in addition thymic and midgut and 1 lung NENs. Liver metastases were observed in 6 (13%) patients. At diagnosis, 29(69%) patients had disease stage 1, 2(4.7%) stage 2, 4(9.6%) stage 3 and 6(14.2%) stage 4. 16(38.1%) patients were submitted to surgery. Other treatment modalities used were: somatostatin analogues (n=9), chemotherapy (n=2), targeted molecular factors (n=2), peptide receptor radionuclide therapy (n=1) and chemoembolization (n=1). During the last follow-up visit, 3(10%) patients with pNEN had died due to causes relative to their disease with mean total survival 126.79 months.

Conclusion: Most patients with MEN1 have late progression and long survival despite the presence of disseminated disease, confirming the necessity of their management from referral centers under multidisciplinary teams.

Keywords: men1
Evolution of Gastroenteropancreatic Neuroendocrine Tumors – Experience of a Romanian Endocrine Clinic

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Introduction: GEP-NETs (gastroenteropancreatic neuroendocrine tumors) are a heterogenous group of tumors. Aim(s): To present GEP-NETs evaluated in our department in the last 10 yrs and review their evolution under available therapies. Materials and methods: The 42 GEP-NET patients included were 24 foregut (9 insulinomas), 8 midgut, 1 hindgut and 9 with unknown primary. Localization was by CT, MRI, colonoscopy or bronchoscopy. Octreoscan was used in a few patients being available only in the last years. Mean period of follow-up was 53.2 months. Results: IHC from tumor or liver metastasis allowed grading of the tumors – 31.5%G1, 47.4%G2 and 21.1%G3. 21 patients with GEP-NETs had carcinoid syndrome. Surgery cured 5/18 patients and somatostatin analogues (SSAs) were used in 23 cases, with disappearance of carcinoid symptoms in 5 and improvement in 16 cases. 3 pts were also treated with radiolabeled somatostatin analogues (PRRT), 1 of them with remission of the disease at 6 yrs after PRRT the remaining 2 with slow progressive disease. 7 cases were treated with chemotherapy and 3 with interferon. Excluding insulinomas, 9 of GEP-NET patients (39.1%) died during the follow-up. From the 9 insulinomas 1 was diagnosed as malignant and 3 had persistent disease after surgery, 2 of them controlled on diazoxide. Conclusion: Multidisciplinary approach is needed for the correct diagnosis and treatment of NETs. SSAs treatment offers improvement of carcinoid symptoms but although progress was made in the last years in this field, mortality is still high. Keywords: gep-nets
The Prevalence of Intestinal Metaplasia in Patients with Gastric Neuroendocrine Neoplasms Type 1

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Introduction: Intestinal metaplasia (IM) of the gastric mucosa is a relatively frequent precancerous lesion. Aim(s): The aim of the study was to assess the prevalence and to find parameters that could predict the presence of intestinal metaplasia in gastric neuroendocrine neoplasms type 1 (GNEN1). Materials and methods: Forty two (34 females) patients with GNEN1 were retrospectively studied. All patients included in the study had positive parietal-cell antibodies and were negative for Helicobacter pylori. All patients underwent a gastroscopy with multiple biopsies. Chromogranin A, gastrin, vitamin B12 and ferritin levels were also assessed. Results: The mean age and follow up were 53.1±14.02 years and 45.32±19.69 months, respectively. At diagnosis, chromogranin A, gastrin, vitamin B12 and ferritin levels were: 34.14±45.16 ng/ml (<110), 897.58±835.86 pg/ml (<110), 450.22±566.1 pg/ml (300-960) and 65.26±74.67 ng/ml (20-350), respectively. Intestinal metaplasia appeared in 33 patients (78.6%) with GNEN1; 30 (91.2%) had large IM and 3 (8.8%) had both small and large IM. In univariate regression analysis none of the parameters studied could predict the presence of intestinal metaplasia. Conclusion: Our study showed a high prevalence of IM in GNEN1. None of parameters studied predicted IM presence. Further clinical studies are required to determine which parameters predict the presence of IM in patients with GNEN1. Keywords: intestinal metaplasia, gastric neuroendocrine neoplasms type 1
Clinical Characterization of Patients with Neuroendocrine Neoplasm of the Appendix in Ireland and in Italy: A Retrospective Study from Two Tertiary Institutions

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Introduction: Appendiceal neuroendocrine neoplasms (aNEN) are rare tumors often diagnosed incidentally at appendectomy. Though most aNEN patients have a positive outcome, distant metastases may rarely occur and the identification of the patients at higher risk is required. Aim(s): To retrospectively collect and analyze histological, clinical, biological and follow-up data of aNENs

Materials and methods: All patients with histologically proven aNENs diagnosed at Mater Misericordiae University Hospital, Dublin and Fondazione IRCCS Ca’ Granda Ospedale Maggiore Policlinico, Milan from 2000 to 2015 were included. Results: 43 patients (25 females, mean age 30 years) were included. All of them had a well-differentiated aNEN. 19 patients had stage I, 10 patients stage II and 6 patients stage III disease. The stage was not defined in 8 patients. Mean tumor size was 11±8 mm. 38 patients underwent appendectomy for appendicitis, 5 had surgery for other conditions. Right hemicolectomy was performed in 8 patients, 3 of which had lymphnode involvement. Median follow-up was 12 months. One patient had disease recurrence with liver involvement. Disease recurrence correlates with lymphnode postivity (p<0.01) and stage (p<0.05) but not with grading.

Conclusion: Most aNENs have a positive outcome after surgery. The only patient who developed distant metastases had lymphnode involvement at the time of surgery and probably required a more aggressive management. Lymphnode involvement and stage correlate with recurrence independently from grading. Keywords: appendix, nen, epidemiology
Pancreatic Involvement in VHL Disease: The Turin Experience

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Introduction: Von Hippel-Lindau disease (VHL) is a rare heritable genetic syndrome. Its typical manifestations concern CNS but it may affect other organs such as the pancreas. Aim(s): Our objective was to study pancreatic involvement in VHL patients to obtain confirmation with current literature. Materials and methods: We included all the patients who referred to our center for follow-up of VHL disease: we considered the ones with pancreatic involvement (simple cysts, SCAs or pNETs). We collected data about patients (demographics and medical history) and about pancreatic lesions (imaging features, histological and cytological analysis). Results: Out of 23 patients, 17 had pancreatic involvement. Multiple simple pancreatic cysts in 12 patients, SCAs in 2 patients and NETs in 6 patients. Mean age 41 (min 25 max 75), 10 males and 7 females. All NETs were G1; 5 were in the head and 1 in the tail. 5 out of the 6 NET patients underwent surgery. No surgery was performed over the 2 SCAs, one in the head and one in the tail. Simple cysts affected 12 patients, mostly in the head. 3 patients underwent surgery for symptomatic disease. Conclusion: 74% of the patients were affected by pancreatic lesions, no sex prevalence. 70,5% suffered from simple cysts, 35,3% from NETs and 11,8% from SCAs. All pancreatic NETs were G1 and behaved in a benign fashion. Surgery was performed in patients with head NET or with symptomatic cystic disease. This study confirms the data seen in literature: younger age of incidence and peculiar frequency in the type of lesions. Keywords: vhl
Clinical Outcomes in Small Neuroendocrine Tumours Treated with Intestinal Surgery in Tertiary Centre

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Introduction: Patients with Small Bowel Neuroendocrine Tumours (SBNET) may require small bowel surgery either as an emergency or electively. Robust data from Tertiary Referral Centres (TRC) are lacking. Aim(s): To assess the short-term outcome, disease progression and overall survival of patients with SBNETs who underwent intestinal surgery in a TRC. Materials and methods: 37 patients with SBNET who underwent intestinal surgery in our unit were retrospectively analyzed. Data included gastrointestinal (GI) symptoms pre-surgery, hepatic/Mesenteric Metastasis (MM) and desmoplasia. Results: 86% had GI symptoms pre-surgery. 70% had hepatic metastases. 81% of all patients had MM, of which 53% were resected along with the primary. In the remaining, MM was not resected either due to severe desmoplasia (28%) or to mesenteric vessel occlusion. 3% had only by-pass surgery. The mean hospitalization period was 11 days. Perioperative morbidity (anastomotic leak) was noted in 5% and mortality was zero. At 12 months post-operatively, 65% had complete resolution of GI symptoms. 21% had disease progression post-surgery (mean time to progression: 19 months). 81% are still alive (mean follow-up: 36 months), whilst 19% died due to tumour progression (mean survival post-surgery: 22 months). Conclusion: Patients who had intestinal resection in TRC had significant symptoms' resolution with acceptable morbidity rates and zero mortality rates. Larger multi-center studies among TRC are needed to identify prognostic factors for short and long term outcomes. Keywords: net, intestinal surgery
Investigating the Increasing Incidence of Neuroendocrine Tumors in Pakistan as a Result of Increased Awareness

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Introduction: Incidence of Neuroendocrine tumors has been increasing worldwide. The reasons for this rising incidence remain unknown. Aim(s): We aim to investigate the increasing incidence of neuroendocrine tumors in Pakistan by assessing the patterns of metastatic presentation and their early detections. We also aim to analyse the increasing awareness about NETs among Pakistani population. Materials and methods: The study was conducted in Shaukat Khanum Cancer and Research Centre, Lahore. Patients with the confirm diagnosis of neuroendocrine tumors were included in the study. The main outcomes considered for the study were overall survival, proportion of metastatic disease, site specific and overall incidence. Knowledge assessment was done by constructing a questionnaire. Results: Four thousand fifteen patients with diagnosed neuroendocrine tumors were identified. The incidence increased from 1.2 to 3.3 per 100,000 per year. The rising incidence was because of advanced diagnostic techniques. Male gender, awareness programs were the factors contributing towards the increasing incidence of neuroendocrine tumors. Conclusion: The study shows that awareness of NETs is the leading cause towards early detection of the tumors. A formal structural approach should be designed to further increase the awareness of neuroendocrine tumors In order to detect them in early stages. Keywords: rising, incidence, awareness, nets, under, developed, country
A Multicenter 10-Year Clinical Epidemiological Study of Rectal Neuroendocrine Tumors in China

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Introduction: Few data can be available for rectal neuroendocrine tumors (NETs) in China. Aim(s): To present clinical characteristics of rectal NETs in Chinese patients and to explore the current treatment approaches for these patients. Materials and methods: All rectal NETs patients were obtained from a hospital-based, nation-wide, and multi-center 10-year (2001-2010) retrospective study of neuroendocrine tumors. All rectal NETs patients were confirmed by pathology in the selected hospitals and information of clinical characteristics was collected based on the designed case report form. Results: 341 male and 254 female cases were eligible. The mean age at diagnosis was 51.3 years. About 77.4% of rectal NETs were diagnosed at the localized stage and most were at grade G1. Rectal NETs, were more likely to be detected at an earlier stage and grade, and tended to be reported in male, nonsmokers, nondrinkers or urban residents or subjects with a higher education level. Most patients had no family history of cancer. Over 90% of patients underwent radical surgery and other therapies were limited, such as chemotherapy, biotherapy, target therapy, and peptide receptor radiotherapy. Conclusion: Rectal NET patients were more likely reported in male, urban residents, and more likely to be diagnosed at the early stage. Radical surgery was the most common used therapy method. Additional studies are needed to further explore the early diagnosis and treatment of rectal NET patients. Keywords: rectal, neuroendocrine, treatment
Epidemiological Factors at Diagnosis in a Large Cohort of Patients with Pancreatic Neuroendocrine Tumours


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Introduction: Pancreatic neuroendocrine tumours (pNETs) are among the most frequent NETs with an increasing incidence. However, recent epidemiological data reports are limited. Aim(s): To present epidemiological data at the time of diagnosis (Dx) in a large cohort of patients with pNETs. Materials and methods: 201 patients from our NET database were included in this retrospective analysis. Dx was defined as the date of the first histopathological data. Results: Mean age at Dx was 60.9 years and 49% were females. 74% had a non-functioning pNET and in 58% the tumour was diagnosed incidentally, whereas 13% had symptoms for over a year pre-diagnosis. Among those with functioning pNETs (n=52), 33% had an insulinoma and 31% a gastrinoma. In 7%, pNETs were associated with MEN-1. 9% had a history of concomitant, different malignancy. In 85%, tumours were avid in Somatostatin Receptor Scintigraphy. 62% had primary tumour >2cm. 53% had no hepatic metastases and underwent primary resection. 21% had hepatic metastases with liver tumour burden <25%, 9% between 25-50% and 8% had >50%. 30% had Grade 1 (G1) pNET, 46% G2 and 24% G3. Mean chromogranin A at Dx was 150.3U/L (N=<27) and in 46% it was within normal range. The median overall survival was 4.6 years with a 5-year survival of 44%. Conclusion: pNETs are predominantly non-functioning, G1/G2 NETs, most diagnosed incidentally or with a delay, which may explain the high metastatic rate at Dx. Prognosis appears favorable in comparison to other malignancies of the pancreas. Keywords: pancreatic neuroendocrine tumors, epidemiology

Neuroendocrinology 2017;105(suppl 1): 1-338
Clinical Significance of Incidental Detection of Appendicular Neuroendocrine Tumours in Sri Lanka

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Introduction: Neuroendocrine tumours are known to occur in the appendix and mostly detected incidentally following appendicectomies for acute appendicitis. Most of them have a benign behavior and no clinically significant biological activity is found. However, the correct recognition of the pathology is of paramount importance as it may need a separate evaluation and management. Aim(s): The objective of this study was to find the incidence of incidentally detected appendicular neuroendocrine tumours, its disease characteristics and impact on the overall patient management. Materials and methods: 462 histopathology reports of appendicectomies done at the Base hospital Homagama over four years were reviewed. All suspected cases on conventional histopathological analysis have undergone confirmation with immunohistocheical evaluation. Results: only 4 patients has had neuroendocrine tumour of the appendix and all are reported as benign carcinoid tumours. All of them have had the clinical diagnosis of acute appendicitis without any clinical features suggestive of carcinoid syndrome. Only one case had the tumour with background acute appendicitis. All were located in the tip of the appendix and maximum size reported is 1.2 cm. Conclusion: Incidence of appendicular neuroendocrine tumours in Sri Lanks (0.86\%)is comparable with reported data. It does not seem to have a significant clinical impact as it is rare, does not have a demonstrable association with acute appendicitis and does not commonly alter the management of patients. Keywords: appendicular net
OPALINE Study: Observational Study in a Real-World Setting of the Systemic Treatment of Progressive Unresectable or Well-Differentiated Metastatic Pancreatic Neuroendocrine Tumors (pNET)

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Introduction: OPALINE Study focuses on patients with pNET. Two targeted therapies (TT) offer new options to treat these patients: mTORi (everolimus) and a multi-targeted inhibitor (sunitinib). Aim(s): Evaluate the impact of both TT vs other treatments (OT) for pNET in a real-world clinical setting. Materials and methods: We expected 150 patients with well differentiated, progressive, unresectable or metastatic pNET, naïve or pretreated (<5 lines). 2 cohorts are opened TT group; OT group (chemotherapy, SSA, interferon-alpha and vectorized internal radiation therapy). Results: As of July, 20th 2016, 76 patients have been included, 25 treated with TT and 51 with OT. Patients (45 males and 31 females) were 61.9 ± 12.03 years old, 97.2% had an ECOG status ≤ 2. 37/75 (49.3%) had received a previous loco-regional therapy of which 29 primary tumor surgery. 72 (94.4%) had liver metastasis. Less than 10% had a functional syndrome. In 1st line, 69.6% had received chemotherapy (C), 21.7% SSA and 8.7% TT. In 2nd line, 28.6% received TT, 28.6% C, 28.6% SSA, and 14.2% OT. In 3rd line, 58.3% received TT, 33.4% C, and 8.3% SSA. In TT group, 6.8% were treatment-naïve, 50%, 27.3%, 27.3% had received respectively 1, 2 or 3 lines prior treatment. In OT group, 39.7% were treatment-naive and 38.1%, 14.3%, 14.3% had received respectively 1, 2 or 3 lines prior treatments. Adverse events observed were expected and similar that reported. Conclusion: Based on expected cohort, this observational study describes routine clinical practice in pNETs. Keywords: pnet, targeted therapies
Prospective Study on the Impact of a Multi-Institutional NET-Specific Multidisciplinary Tumor Board on Individual Treatment Plans

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Introduction: A multi-institutional health network (nine hospitals) was set up in the Belgian Antwerp-Waasland region for the multidisciplinary care of gastroenteropancreatic neuroendocrine tumor (GEP-NET) patients, called “NETwerk”. Local multidisciplinary teams refer all GEP-NET patients to be discussed among specialists, experienced in NET diagnostics and treatment, at a NET specific multidisciplinary tumorboard (MDT). Aim(s): An interim analysis to determine the efficacy of the NET specific MDTs (biweekly) within “NETwerk” in altering the treatment plan of NET patients

Materials and methods: In a prospective study in 146 consecutive patients discussed at the NET specific MDTs, local treatment plan and with the treatment plan after discussion within “NETwerk” were compared. Results: The NET specific MDT treatment plan differed in 30% of the cases (n=44) from the local MDT plan. In 18 out of these 44 cases, the local MTD proposed a follow-up whereas the NET specific MDT required a change to: chemotherapy (n=1), surgery (n=3), SSA (n=2), further diagnostic (n=10) and cured (n=2). For 102 NET cases, both treatment plans were the same with the majority being follow-up (n=34) and SSA (n=20) Conclusion: “NETwerk” addresses the needs of both new and follow-up NET patients. In contrast with local MDT decisions, centralized NET specialists frequently propose further diagnostics such as DOTANOC or other additional imaging, echo-endoscopy, genetic screening. This leads to a individual tailoring of NET specific management. Keywords: care networks, quality
Launching NETwerk: Diagnosis and Treatment of Neuroendocrine Tumors within a Multi-Institutional Collaboration in the Region of Antwerp-Waasland in Belgium


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Introduction: Centralizing cancer services is one way to improve global outcome for cancer patients but brings along that patients must be motivated to travel and that doctors of local hospitals get deprived of the diagnostic and treatment skills. The alternative way is to centrally coordinate cancer services across different hospitals. In this scenario, local multidisciplinary teams refer all patients to be discussed among cancer specialists. This continuous feedback system also creates the opportunity to propose additional more specific and sensitive examinations for individual patients which would introduce the end of local substandard treatment. Aim(s): The aim is to launch a horizontal hospital collaboration creating a Belgian network for neuroendocrine tumor patients called “NETwerk”. Materials and methods: NET-specialists from nine different hospitals in Belgium provide optimal NET-management in a collaborative setting and according to ENETS guidelines. A NET-specific tumorboard operates by videoconferencing. Local teams enroll every NET-patient in “NETwerk” to be discussed. Subsequently, local caregivers receive feedback from the NET-specialists Results: During the first eight months, 81 new diagnosed NET-patients and 21 follow-up cases were discussed. Diagnostic examination and treatment assessment are synchronized with local hospitals to assure NET-patients receive optimal disease management. Conclusion: The approach of “NETwerk” can compete with centralized patient care in designated centers. Keywords: quality, treatment plan, network
Liver Metastatic Disease (LMD) in Gastroenteropancreatic Neuroendocrine Tumors (GEP-NET): Incidence, Treatment and Survival in a Multicenter Study in Argentina. Preliminary Report. ARGENTUM GROUP

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Introduction: The first observational Study from our Group in Argentina, showed 60% incidence of liver mets at initial diagnosis. The treatment encompasses a wide scope of surgical and non-surgical modalities. Aim(s): To assess prevalence, incidence and regional trends in management and outcomes in patients with LMD in GEP-NET. Materials and methods: Data was registered online and assessed for internal consistency by reviewers from our working group. We included only patients with synchronous or metachronous LMD. Results: The study comprised 271 patients diagnosed with LMD. The median age was 61 years and 51% were men. Primary tumor locations were: small bowel (41%), pancreas (33%), unknown primary (13%), colorectal (5%) and esophageal/gastric (5%). Stage: II (4%), III (11%), IV (85%). 47% were grade 1, 39% grade 2 and 9% grade 3. 26 pts. based on ENETS Classification (11%) had Type I Liver disease, 42% Type II and 47% diffuse pattern (defined in clinical practice). Synchronous (79%), metachronous (21%). Resection of the primary tumor was performed in 46%, and 38% underwent liver surgery. Loco-regional therapies were used in 16%. 34% received systemic treatment, 72% received at least 3 lines of treatment. 83% of patients were alive at 5 years and 75% at 10 years. Conclusion: Patients with GEP-NET often present with liver mets at time of diagnosis. This is the first study in our Country that describes different lines of treatment used in a contemporary series Multidisciplinary approach can optimize therapeutic strategies. Keywords: liver, nets
Observational Study of Small Pancreatic Neuroendocrine Incidentalomas: A Tertiary Referral Center Experience

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Introduction: Incidence in small pancreatic neuroendocrine incidentalomas (PNETs-I) are increasing and its management remains controversial. Aim(s): A descriptive analysis of all patients and a comparative study between observation group (OG) vs resection group (RG) was made. Materials and methods: Since March 2000, 46 patients with non functioning PNETs-I ≤30mm were evaluated in our center. Results: 36 patients in OG and 10 in RG were evaluated. Median follow up (months) was 35.9 in OG and 76.6 in RG. 69.9% were diagnosed in the last 6 years. Mean age (years): 69.5 in OG and 57 in RG (p<0.003). 56.5% were women. Mean tumor size (mm) was 12.5 (11 in OG vs 18.7 in RG p<0.005). PNETs-I were multiple in 17.4% cases. At diagnosis, all PNETs-I’s size were ≤2cm in OG, without metastases. In RG, 80% had surgery complications, mostly mild to moderate without deaths. Diagnosis was made by imaging procedures in 91.6% of OG. In our series, 82% had a CgA assessment at diagnosis. Median CgA value was 179µg/L (72-304). At the end of follow up, 88% in OG of patients had no change in tumor size, the rest had tumor growth <20%; no PNETs-I resection were needed, and none of the patients metastasized or died because of PNETs-I in this group. Conclusion: Our study showed an increasing incidence of non functioning PNETs-I. By the end of the study, no patients developed metastases and significant growth and neither of them died from PNETs-I in OG. Active surveillance is safe in selected PNET-I patients. Prospective multicentric studies are needed to confirm our results. Keywords: pnets
NET – Incidental Findings: Small, Silent and Innocent?

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Introduction: Neuroendocrine tumours (NETs) are rare neoplasms, with an overall incidence of 2 cases per 100,000 individuals per year. This number is increasing due to improved diagnosis, classification and higher imaging sensitivity, which lead to discovering of small and clinically insignificant NETs.

Aim(s): Assess treatment approach after incidentally diagnosed NET.

Materials and methods: Retrospective, descriptive study of patients incidentally diagnosed with NET in our institution between April 2012 and December 2016.

Results: Of 57 patients diagnosed with NET, 22 (39%) were incidentally diagnosed (median age 65). Of this, 12 (55%) were male. Diagnostic method: endoscopic- 8 (36%), imagiologic– 7 (32%) and histological exam– 7 (32%) patients. Primary tumour location: duodenum 6 (27%), pancreas 5 (23%), small bowel 3 (13%), appendix 2 (9%), colon 2 (9%), stomach 1 (5%), rectum 1 (5%), unknown localization 2 (9%). WHO classification: G1– 8 (36%) cases, G2– 9 (41%), G3- 2 (9%), 3 (14%) undetermined. Five (23%) cases were metastatic at the time of diagnosis, 10 (45%) patients were submitted to surgery, 4 (18%) to polipectomy, 2 (9%) to chemotherapy. We considered as overtreated 3 (17%) cases and 8 (36%) did not needed further treatment. Mortality: 5 (23%) cases.

Conclusion: Incidentally discovered NETs represent a clinical dilemma: what is the best treatment approach? Some will benefit from an early diagnosis, when others will be overtreated. A multidisciplinary teamwork is crucial to an individualised patient management.

Keywords: net, incidentaloma
(F17)
Abdominal Obesity, Fasting Glucose and Metabolic Syndrome Are Risk Factors for Well Differentiated Digestive Neuroendocrine Tumors

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Introduction: Digestive NETs (DNETs)’s incidence has increased last 40 years. Visceral obesity and metabolic syndrome (MetSyn) were recently reported to be associated with several cancers, although not so far with DNET. Aim(s): To explore the possible relationship between obesity, MetSyn and well-differentiated (WD) DNETs by undertaking a case-control study. Materials and methods: Patients with GI-NETs or pNETs (n=96) were recruited from Endocrine Tumors Clinic of IPO Porto and cross-matched with a control group (n=96) derived from the PORMets study, a nationwide epidemiological study that assessed MetSyn prevalence in the general population, pair-matched for age, gender and place of birth. MetSyn was defined using the JIS criteria. DNET were classified according to primary tumor localization, hormonal secretion, TNM stage and WHO grading. Results: Primary tumors were GI-NETs (75.0%) or pNETs (22.9%). Hormonal syndrome was present in 45.8%. Grading defined 66.7% G1 and 27.1% G2 tumors. Disease was localized in 31.3% of patients; locoregional in 16.7% and disseminated in 43.8%. WC $\geq$ 80 cm (female) or 94 cm (male), TG $\geq$ 150 mg/dL, FG $\geq$ 100 mg/dL and MetSyn were found to be RF for WD-DNETs (OR 2.5 1.4-4.6 95%, p<0.002; OR 2.2 1.2-4.1 95%CI, p=0.011 and OR 4.3 2.3-8.2, p<0.001 and OR 2.4 1.3-4.3 95%CI, p=0.003). Risk higher if $\geq$ 4 criteria. Conclusion: If further confirmed, association of visceral obesity, FG and MetSyn with WD-DNETs opens new perspectives for treatment and prevention of these tumors. Keywords: neuroendocrine tumors, metabolic syndrome, visceral obesity
Clinicohistopathological Features and Treatment Outcomes of Neuroendocrine Tumors; A Single Center Experience

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Introduction: Neuroendocrine tumors (NETs) are very heterogeneous family of cancers. Tumor and patient characteristics of NETs significantly change between geographical locations that probably induced by environmental and genetic factors throughout the world. Therefore, reporting single center experience may help to clarify epidemiological view and to improve the decision-making process. Aim(s): we aim to the study demographic characteristics, the overall, stage, and site-specific outcomes, prognostic factors, used treatment modalities and outcomes in 82 patients with NETs those who were followed in our center. Materials and methods: We performed a retrospective analysis of 82 patients of NETs those who followed by Baskent University, to record patients and tumors characteristics, treatment modalities and prognostic factors. Results: Median age was 55 years old. Mean follow-up period was 21.3 months. Median overall survival (OS) time for all group and localized NETs, were 44 and 24 months, respectively. The most common primary site was found as a gastrointestinal system and then pancreatic region. Liver metastasis was far the most common metastatic site. Over 70 percent of patients were treated with chemotherapy and somatostatin analogs. Conclusion: Patients with higher grade, male gender, and advanced age (>65 years old) had reduced survival rate. However, relatively small number of patients and less usage of (<10%) of new treatment modalities created limitations for producing future directions from our study. Keywords: neuroendocrine tumors, single center
Clinicopathologic Characteristics and Survival of Patients with Gastro-Enteropancreatic Neuroendocrine Neoplasm (GEP-NEN) in a Multi-Ethnic Asian Institution

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Introduction: Recent findings suggest epidemiologic differences in gastro-enteropancreatic neuroendocrine neoplasm (GEP-NEN) between population studies. Aim(s): We evaluated clinicopathologic characteristics of GEP-NEN in a multi-ethnic Asian institution. Materials and methods: This is a retrospective study of patients diagnosed with GEP-NEN at a tertiary medical institution at Singhealth Outram Campus, Singapore between 1995 and 2015. Results: Two hundred ninety-five patients were included. The racial distribution was: Chinese (74.6%), Malay (4.4%), Indian (9.5%) and others (11.5%). Median age at diagnosis was 59 with 52.5% being males. Distribution of disease stage at diagnosis was: local (42.4%), regional (15.3%) and distant (38%). Pancreatic primary was most common (42.6%), followed by rectum (19%) and stomach (9.8%). Primary tumor site varied significantly by race. Age at diagnosis also varied significantly by race and site of primary tumor. Malay patients were younger (median 42 years) at diagnosis than Chinese (60 years). Patients with appendiceal NEN (48 years) was younger compared to esophageal NEN (66 years). Disease stage correlated with primary tumour site and grade (p<0.01). Median survival for all GEP-NEN was 10.2 years. Age at diagnosis, stage, primary anatomic site and differentiation were prognostic for OS in multivariate analyses. Conclusion: Pancreatic primary is the most common site of GEP-NEN. Primary tumor site and age at diagnosis varied by race. Prognostic factors identified are similar to other series. Keywords: carcinoid
Sequence of Therapy and Survival among Advanced Pancreatic Neuroendocrine Tumors (pNETs)

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Introduction: Therapy for advanced pNETs involves surgery (SG) and non-SG options, including liver ablation (ABL), systemic therapy (ST), somatostatin analogues (SSA). Optimal initial therapy is unknown. Aim(s): We describe sequence of therapy for pNETs and survival differences between treatment cohorts. Materials and methods: Sequential patients with advanced pNETs referred to the BC Cancer Agency between 2000-2013 and received at least one treatment modality were reviewed. SG included any resection of primary or distant disease; ST included chemo- and small molecule therapy, and peptide receptor radiotherapy. Results: Of 86 cases, median age was 61.1 years (IQR 50.4-68.2) and 49% were male, with median overall survival (OS) of 45.8 months (95% CI 28.3-63.4). Initial treatment was SG (33%), ABL (0%), ST (41%), and SSA (27%). Initial SG vs. non-SG therapy was associated with increased median OS (155 vs 21.1 months; p<0.01) and median progression-free survival (22.2 vs 4.2 months; p<0.01). Median OS was 16.0 months (95% CI 6.4-26.7) and 44.4 months (95% CI 12.6-76.2) for ST and SSA cohorts, respectively (p=0.001). 3% of non-SG patients received subsequent SG and 14% received subsequent ABL. 48 patients (56%) received >1 line of therapy and there was no difference in OS or PFS between second-line therapies. Conclusion: Advanced pNET patients eligible for initial SG demonstrate an improved OS. Upon progression, choice of second-line therapy was not prognostic and may be chosen based on disease and patient characteristics. Keywords: pnet, sequential therapy
Concomitant Intraductal Papillary Mucinous Neoplasms and Neuroendocrine Tumors of the Pancreas: More Than Just a Coincidence?

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Introduction: Intraductal papillary mucinous neoplasms (IPMNs) and pancreatic neuroendocrine tumors (pNETs) are rare tumors. Up to now 14 patients with association of endocrine and exocrine neoplasms of the pancreas have been reported in literature: this association is not expected to be frequent Aim(s): We looked for any common findings between these two entities that could help early recognition and further comprehension of this association Materials and methods: 6 patients in our clinic suffer from IPMN and concomitant pNET. We collected data about the patients (age, sex, symptoms, medical history, blood chemistry, type of imaging) and about the lesions (classification, dimension, localization, imaging features, fine-needle aspiration (FNA) biopsies results and histology) Results: All patients (3 M - 3 F) were asymptomatic. Average age at diagnosis was 52. All IPMN were branch duct, 4 in the head and 2 in body-tail, medium ductal diameter 12mm (min 8 max 16 mm). All NET underwent EUS with FNA, all were non functional G1 positive for CgA and NSE staining; 4 in the body and 2 in the head, medium diameter 11mm (min 6 max 15 mm). The first diagnosis was NET in 3 patients and IPMN in the other 3. Conclusion: No sex or age predisposition was found, nor predominant localization or common background. No other neoplasms were found. Indolent behavior up to now. Although IPMN and pNET concomitance is not too large in literature and no diagnostic hallmark were found, it is still to be proven that this association is just fortuitous. Keywords: ipmn, net, pancreas
Assessment of Small Intestinal Bacterial Overgrowth (SIBO) in NET Patients

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Introduction: SIBO is not uncommon in NETs. Hydrogen Breath testing (HBT) using glucose may be more sensitive to proximal SIBO as glucose rarely reaches the colon. Many NET patients are likely to have distal SIBO however, as factors such as ileocecal valve removal apparently increase distal SIBO risk. Thus glucose BT alone may limit sensitivity for detecting SIBO in some NET diagnoses. Aim(s): Assess likely risk factors for SIBO. Assess sensitivity of additional lactulose HBT and CH4 BT.

Materials and methods: Retrospective data (n=55) of NET patients undergoing HBT was examined. Twelve patients (12/55) who tested negative for glucose HBT but continued to have diarrhoea +/- wind had repeat BT using lactulose. These patients had both H2 & CH4 BT.

Results: Midgut NET diagnoses were most frequently referred for BT (n=43, 78%). Twenty four (24/55, 44%) had prior right hemicolecotomy. Ten (10/24, 42%) of those were SIBO positive. Ten patients were positive for HBT prior to being given the glucose substrate, they all had abdominal surgery in the past. Twelve patients who tested negative for glucose HBT had repeat testing using lactulose and measured both H2 and CH4 production. This led to an additional 3 (25%) positive results.

Conclusion: Abdominal surgery, especially right hemicolecotomy increases the likelihood of a positive glucose HBT. Glucose may still be sensitive in those with risk factors for distal SIBO. Additional lactulose use with H2 and CH4 measurement increases the sensitivity in diagnosing SIBO.

Keywords: nets, sibo, dysbiosis,
Prognostic Relevance of Pancreatic Neuroendocrine Tumors Grading on EUS-FNA

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Introduction: Since WHO 2010, resected pNETs are graded as G1, G2 or G3 using the Ki67-LI. EUS-FNA is often used for diagnosis but few studies have assessed its value for grading. Aim(s): To compare Ki67-LI obtained on cytology (cG) with histology (hG). To assess: a. the influence of tumour size, and number of counted cells on FNA grading; b. the overall survival (OS) and progression free survival (PFS) of patients based on cG. Materials and methods: EUS-FNA was performed for 102 pNETs (57 resected), retrospectively included in this multicentre study. cG (200 cells counted) was done on all FNAs. For 29 FNAs, > 2000 cells were counted (14 resected). Comparison was made between hG and cG for the 57 resected patients. Patients were followed-up until 06/2016. Results: cG was consistent with hG in 39/57 pts, with a concordance rate of 72%, using a Ki67 5% cut-off for G1/G2. For Ki67-LI absolute values, correlation was \( r=0.443 \), which raised to \( r=0.824 \) (\( p<0.001 \)) when only FNAs with >2000 cells were counted. 21/22 pNET <2 cm had same grading on cG and hG, whereas it was discordant for 15/16 pNET >2 cm. 38 patients died after a 70.5 m f-up. OS for the whole cohort was 235 m, and differed between cG1 (235m), cG2 (36,3m) ad cG3 (10,9m). Conclusion: Our results indicate that pNET cG is more accurate when tumors are <2 cm and more cells are counted on FNA. Discrepancies are seen among G2 tumors, often considered G1 on FNA, due to tumor heterogeneity. EUS-FNA is valuable to distinguish patients with good (cG1) and poor (cG3) prognosis. Keywords: eus-fna, ki67, pnet, os
Two Separate Modified ENETS Staging Classifications Are Needed for Duodenal and Jejunoileal Neuroendocrine Neoplasms

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Introduction: Previous studies showed duodenal neuroendocrine neoplasms (d-NEN) and jejunoileal NEN (j-NEN) harboring different features. However, the staging classifications of d-NEN and j-NEN proposed by ENETS are identical. Aim(s): To compare the clinicopathological features between d-NEN and j-NEN and investigate the prognostic validity of ENETS staging classifications. Materials and methods: 1076 d-NENs and 2941 j-NENs patients were retrieved respectively from Surveillance, Epidemiology, and End Results (SEER) cancer registry. Disease-specific survival was used as the main outcome. Results: The age at diagnosis of patients with d-NEN tended to be older than patients with j-NEN (62.5 vs. 60.1; P<0.001). Tumor size of d-NEN was significantly smaller than that of j-NEN (1.3 cm vs. 2.1cm; P<0.001). T1/T2, N0, M0, stage I/II disease were more common in d-NEN while advanced disease was more common in j-NEN. Different defects of ENETS staging classifications were found. In d-NEN, patients with T1 and T2 and patients with stage I and stage II had similar survival. While in j-NEN, N status did not impact survival. Patients with stage I, stage II and stage III had similar survival. Conclusion: The clinicopathological features of d-NEN and j-NEN are quite different. The ENETS staging classifications for d-NEN and j-NEN have different defects and two modified staging classifications are needed. Keywords: stage, duodenum, jejunoileum, neuroendocrine neoplasms
Pancreatic Neuroendocrine Tumors in MEN1 Disease: A Monocentric Longitudinal and Prognostic Study

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Introduction: In MEN1+ patients (MEN+), pNETs are considered to be high risk for multiple, malignant and aggressive tumors. Aim(s): To describe clinical and prognostic pNET in MEN+ Materials and methods: To compare pNET in MEN+ with cG/hG-adjusted pNET in MEN- Results: pNET occurred in 13/16 MEN1+ (G1:4/G2:4/Ia:10/IIb:2/Iib:1). pNET was considerate stable in 10 pts and resolved in 3 pts, trough surgery in 4 pts and somatostatin analogues therapy in 9 pts. Age at diagnosis was significantly lower in MEN+ (p<0.001), independently from pNET functional subtypes, cG (Ia:p=0.01/IIa=0.04) and hG (G2:p=0.05). pNET functional subtypes do not differ between MEN1+ and MEN- (Insulinomas:2 MEN+ and 10 MEN-/Non function pNET: 11 MEN+ and 22 MEN- p=0.03). Histological and clinical tumor grade and Ki67 were superimposable in MEN+ and MEN-. Multifocal pNET occurred in 12 of 13 MEN+ and correlated to higher risk of MEN1 disease (p<0.001; OR:116, 95IC: 10.9-1229), independently from the cG (Ia:p<0.001; OR:10, 95IC:1.5-64/IIb:p=0.04) and hG (G1:p=0.004/ G2: p<0.002). In hG-G1, cG-Ia and lb MEN+ and MEN-, no recurrence or disease progression occurred. In hG-G2 pts, 13 progression-disease events occurred (4 in MEN+/7 in MEN- p=0.14). A part of progression, also progression-disease-survival time was superimposable in MEN+ and MEN-, after adjusting for hG and cG. Conclusion: Applying a standardized treatment strategy, pNET in MEN+ and MEN- do not differ for prognosis but only for clinical features, as younger age at diagnosis and multifocality. Keywords: pNETs, men, prognosis
Exploring the Pathological and Clinical Characteristics of Neuroendocrine Tumors Located in Pancreas

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Introduction: Neuroendocrine tumors are extremely rare and can be found anywhere in the body. Pancreas is the 2nd most common location where neuroendocrine tumors arise. Aim(s): Our study aims to find the pathological and clinical features of neuroendocrine tumors located in pancreas. Materials and methods: The study was conducted in Shaukat Khanum Hospital, Lahore. 16 patients were identified who are diagnosed with pNET. Clinical, pathological and anatomical variables were evaluated. Data was analyzed using SPSS 16.0. Results: Sixteen patients (68%men and 32% women) were studied. 7 patients had type 1 multiple endocrine neoplasia. 12 patients (75%) presented with the typical features of pNET. Most common location was pancreatic tail 62% followed by head of pancreas 38%. Mean tumor size was of 4cm. Diagnostic techniques like CT 48% MRI 36% and others 16% were used for the identification of tumors. Following classification of tumors were made as insulinomas 34.5%, non secreting pancreatic tumor 29.3%, gastrinoma 21.2% and somatostatinoma, glucagonoma 15%. Immunohistochemical markers were positive for Insulin, glucagon, gastrin, somatostatin and PTHrp. Hepatic metastasis was seen in 9 patients. Conclusion: Typical symptoms are produced by pancreatic neuroendocrine tumors. They have high proliferative index which is seen in anatomical and pathological studies. Liver is seen as the most affected gland by advance metastasis of pNET. Because the suspicion of such kind of tumor is low, this leads to the delay in diagnosis of pNETs. Keywords: pNETs, diagnosis
Is Ki67 Index in Biopsy Tissue Truly Reflect Grading of Pancreatic Neuroendocrine Neoplasm?

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Introduction: Ki67 index is essential for progression and treatment of pancreatic neuroendocrine neoplasm (pNEN). For advanced pNEN patient (pts), Ki67 scoring by core/fine-needle biopsy is used to evaluate pNEN pts’ grade. Aim(s): we retrospectively analyzed Ki67 index difference between surgery and biopsy tissue of pNEN pts. Materials and methods: pNEN pts who had both surgery and core/fine-needle biopsy pathological results was performed in single Center. Results: 18 pNEN pts (male vs female: 10 vs. 8) were collected. 10pts had fine-needle biopsy and 8 had core needle biopsy. 11pts were stage IV with type I liver metastasis, 4pts were stage III and 3 were stage II. The grade of surgery pathology was G1 in 3pts, G2 in 11pts, and G3 in 4pts. The grade in pre-operative biopsy tissue was G1 in 5pts, G2 in 7pts, and 6pts with fine-needle biopsy had reported adenocarcinoma with no enough tissue for Ki67 scoring. All pts with core needle and 4pts with fine-needle biopsy had Ki67 index. Compared Ki67 index in surgery tissue with biopsy tissue, 2pts had the same Ki67 index in core needle biopsy and surgery tissue, 10pts had higher Ki67 index in surgery tissue compared with core/fine-needle biopsy tissue, with 4 pts up-graded after surgery (3 pts re-diagnosis from G1 to G2, 1 from G2 to G3). The Ki67 index in surgery tissue was higher than in biopsy tissue (p = 0.001). Conclusion: Ki67 index by biopsy tissue may be underestimated. pNEN pts cannot be operated need more tissue by core needle biopsy for accuracy Ki67 index Keywords: pnen, ki67, biopsy, surgery
Pathological Features of High Proliferative Activity Neuroendocrine Tumor

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Introduction: High Proliferative Activity Neuroendocrine Tumor (NET G3) is difficult to be distinguished from neuroendocrine carcinoma. However, there are differences in clinical treatment and prognosis between the two. So it is crucial to make an accurate pathological diagnosis. Aim(s): The purpose of this study is to investigate the clinical pathological features of NET G3.

Materials and methods: The wax block of 10 NET G3 patients who were diagnosed between January 1st, 2010 to October 31th, 2016 in Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College were collected and stained. Results: 10 cases were included. The tumors located in pancreas (3), stomach (2), liver (2), ampulla (1), colon (1), and gallbladder (1). The Syn (85.7%), CD56 (83.3%) and CK (87.5%) showed strong positive. For expression of P53, 4 cases were negative, and 4 cases weakly positive. The Ki-67 proliferation index ranged from 30% to 60%, averaging 40%. The average value of mitotic count was 7.1/10HPF.

Conclusion: NET G3 had good form and order, with mitotic count being less than 20/HPF and necrosis being not common, but the Ki-67 proliferation index was high, averaging 40%. The expression of CK is strong positive and P53 is negative or weakly positive. Keywords: high proliferative activity, neuroendocrine tumor, pathological feature
Introduction: The expression of cytokeratins (CK) 7,19 rarely occurs in the low grade neuroendocrine tumors (NET) of lung and pancreas. It is known that part of the low grade typical (TC) and atypical (ATC) carcinoids of lung and pancreas (pNET-G1, G2) can progress quickly and metastasize. It is important to distinguish NET with a less differentiated cells immunophenotype.

Aim(s): To examine of the expression of CK 7 and 19 in NET.

Materials and methods: The expression of CK7 and 19 was examined by immunohistochemistry method in to 339 NET: 49 TC, 32 ATC, 60 small-cell (SCC), 11 large cell neuroendocrine carcinomas of the lung (LCC); 78, 98 pNET-G1 and G2 (respectively), 11 pNEC-G3.

Results: The most common expression of CK7, 19 meet in LCC – 72.7 and 90.9%, less frequently in AC and SCC – 50 and 53.3%; 41.7 and 64.6% of cases (respectively), and more rarely in the TC – 5.9 and 15.9%. The frequency of the expression CK7,19 was statistically significantly smaller in the TC than in the ATC, SCC and LCC (р<0.05). The expression of CK19 were significantly more observed in LCC, than SCC and ATC (р <0.01). All pNETs were CK7-negative. CK19-positive were in 14/78 (17.9%), 62/98 (63.2%) pNET-G1,G2 respectively and 100% pNEC-G2.

Conclusion: The expression of the cytokeratin 7 and 19 in low grade neuroendocrine tumors of the pancreas and lung may be helpful to select the patient with less favorable clinical prognosis.

Keywords: neuroendocrine tumors, cytokeratin 7, 19 expression, lung, pancreas, prognostic factors
(G8)
Increase of the Ki67 Proliferation Index over Time in Patients with Neuroendocrine Neoplasms

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Introduction: Whether the Ki67 index increases over time in relation to progression is scarcely studied. Aim(s): We investigated if Ki67 increased in patients with confirmed progressive disease. Materials and methods: Thirty-five patients (21 men) with a median (range) age of 60 (39-76) years and a Ki67 < 20% at diagnosis and an increase of ≥8% at progression were included. The Ki67 was determined in hot spot areas either in surgical specimens or core biopsies from primary tumor or metastases at diagnosis and at progression evaluated by CT or SRI. Results: The primary tumor was located in the pancreas (10), small intestine (17), or other organs (8). Ki67 increased from median (range) 4% (1-18%) to 25% (10-90%) (p<0.001). At diagnosis 14 patients had G1 NET and 21 had G2 NET. At progression 16 had G2 NET and 19 had G3 NEC. The interval between the two Ki67 determinations was 50 (4-211) months. At diagnosis Ki67 was determined in the primary/liver in 22/13 and at progression in 5/30. The discrepancy was mainly due to resection of the primary tumor between the two Ki67 determinations. Conclusion: Ki67 may increase over time and with progression it seems important to obtain a new Ki67 value for adjustment of treatment. Ki67 in the primary may differ from later metastases – which generally have a higher Ki67. Keywords: neuroendocrine, ki67, progression
Sporadic Gastric Neuroendocrine Neoplasm Include Two Different Subtype—Two Histologically and Clinicopathologically Distinct Entity

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Introduction: Gastric Neuroendocrine neoplasm (gNEN) are rare and include several entities. Sporadic gNEN may show heterogenous clinico-pathologic features, but data are limited. Aim(s): To compare the histological, immunohistochemical and clinico-pathologic patterns between type III and type IV NEN. Materials and methods: We retrieved 111 gastric sporadic NEN treated between 2006 and 2014, excluding amphicrine carcinoma and MANEC. Results: 19 cases of type III and 92 cases of type IV gNEN were identified. Compared to type III, type IV showed larger mean size (4.5cm vs 1.8cm) and higher rates of proliferation grade (Ki67 index >20% in 92% vs 15%), LVI (61% vs 11%), invasion beyond muscle propria (75% vs 16%), and local LN metastases (80% vs 16%), (p<0.05% for all differences). 3 type III NEN showed distant (liver) metastases, and 2 died of disease. 19 Type IV showed distant metastases at diagnosis, and 25 died of disease. Histologically, type III was characterized by the presence of microlobular, microacinar or thinly trabecular structures (90%). IHC, extensive to 100% of tumor cells reactivity for p53/Rb in 37% of cases (vs 93% of type IV cases). Type IV lacked membrane expression of SSTR2/5 in 68% of tested cases (against 20% of type III), while both retained expression of CK19. Conclusion: Most type IV gNEN harbor distinct clinical and histological features as well as higher invasive and histological features as well as higher invasive and metastatic potential, making their distinction from type III clinical relevant. Keywords: sporadic, nec, net
Prognosis and Incidence in Pancreatic and Gastrointestinal Neuroendocrine Neoplasms with Emphasis on “NET G3”: An Analysis of 198 Cases from Japan

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Introduction: Prognostic impact of well differentiated pancreatic neuroendocrine neoplasms (PanNENs) with a Ki67 >20%, provisionally called NET G3, needs to be validated and compared to poorly differentiated neuroendocrine carcinomas (NECs). Moreover, the frequency of NET G3 among gastrointestinal NENs (GI-NENs) has so far not been studied. Aim(s): The prognostic impact of NET G3 in PanNENs, as well as in GI-NENs, was investigated. Materials and methods: 122 resected PanNENs and 76 GI-NENs from Japanese patients were histologically graded according to WHO 2010, and a provisionally defined NET G3 category added. The results were correlated with relevant clinicopathologic data. Results: 74 PanNENs (61%) were classified as NET G1, 40 (33%) as NET G2, 6 (5%) as NET G3, and 1 (1%) as NEC. NET G3 had a shorter disease free survival (DFS) than NET G1/2 (p<0.001). The PanNEC case showed a shorter overall survival and DFS than the NETs G3. 47 GI-NENs (62%) were classified NET G1, 11 (15%) NET G2, 1 (1%) NET G3, and 13 (17%) GI NEC. Conclusion: This study from Japan revealed that PanNET G3 patients have a significantly shorter survival than NET G1-2 patients and seem to do better than PanNEC patients. These results were also consistent with the proposed separation PanNET G3 from PanNET G1-2 and PanNEC. GI-NETs G3 appear to be much rarer than PanNETs G3, whereas GI-NECs are significantly more common than PanNECs. This further supports the notion that PanNENs and GI-NENs are biologically two distinct tumor groups. Keywords: net g3, gep-nen, gi-net
Classification of Lung Neuroendocrine Neoplasms (Lung-NENs) According to WHO 2010 for Gastroenteropancreatic NENs (GEP-NENs) Has Prognostic Relevance and Includes Lung-NETs G3


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Introduction: The classification of lung neuroendocrine neoplasms (Lung-NENs) according to the WHO classification 2010 for GEP-NENs, including a provisional category for Lung-NET G3 with Ki67 >20%, may have prognostic implications. Aim(s): The prognostic impact of WHO 2010 classification including the NET G3 category was investigated in Lung-NENs. Materials and methods: 213 surgically resected Lung-NENs from Japan were histopathologically re-evaluated and the data correlated with survival. Results: 38 (18%) cases were classified as NET G1, 17 (8%) as NET G2, 2 (1%) as NET G3, 156 (73%) as poorly differentiated neuroendocrine carcinomas (NEC). 36 (92%) of NETs G1 were typical carcinoids (TC), 14 NETs G2 (82%) were atypical carcinoids (AC), and 2 (100%) NETs G3 were AC. Of the NECs 51 (33%) were small cell NECs and 105 (67%) were large cell NECs. WHO 2010 (NET G1/G2 vs NEC), age (≥65), smoking index (≥500), tumor size (≥20mm), pT (≥pT2), and pN (≥pN1) were associated with shorter overall survival, of which WHO 2010, age, and pN were independent prognostic indicators. Mitotic and Ki67 index of NETs G3 (mean 8.5 and 23, respectively) were both lower than those of NECs (77 and 77, respectively). Conclusion: Lung-NEN classification according to WHO 2010 had prognostic impact. Lung-NETs G3 corresponded to AC and was differed from Lung-NECs. This suggests that Lung-NENs, like GEP-NENs, include NETs that overlap in their proliferative activity with NECs, but differ regarding prognosis and probably also therapeutic responsivness. Keywords: lung nen
Immune-Related Factors Analysis Enhances the Stratification of GEP-NENs Patients into Distinct Prognostic Subsets


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Introduction: Gastroenteropancreatic (GEP) neuroendocrine neoplasms (NEN) are divided into different prognostic categories according to Ki67 class (≤2%: 2%-20%; 20%-55%; >55%); treatment strategies based on this classification are not fully effective. Aim(s): Prognostic role of immune-related markers has not been investigated. Materials and methods: We characterized by IHC primitive tumors and surrounding stroma from 136 GEP-NENs patients (pts). A validated quantitative score combining expression and intensity was used. Prognosis was evaluated in terms of disease-free survival (DFS). Variables were selected according to their significance in a random forest (RF) model and further analyzed with multivariable Cox model to predict 5-year DFS. Results: Significant factors at univariable Cox analysis were nuclear β-catenin score, HLA-Class I and COX2 (p<0.001) in tumor, and PD1, HLA-DR, pS6, CD8, NGFR, PDL1, HLA-Class I, and COX2 (p<0.05) in stroma. The RF model selected β-catenin (p<0.001) in tumor and PDL1 and HLA-Class I (p<0.05) in stroma cells. For explorative purposes, we segregated worst prognosis pts (ki67>55%) and further stratified the remaining ones in 3 categories according to marker predicted DFS (≤10%; 10-40%; >40%). Such categorization achieved high discriminative ability (Harrell’s C=0.773 vs 0.768 of ki67-stratification). Conclusion: In GEP-NENs pts, combining ki67 and immune-related markers may uncover new prognostic subsets compared with Ki67-only based classification. Keywords: ki67, immune-related markers, disease-free survival, pd-l1
Well-Differentiated G1/G2 Pancreatic NETs Can Evolve Towards G3 Tumors

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**Introduction:** Well-differentiated G1/G2 pancreatic NET (pNET) may evolve towards well-differentiated G3 pNET or carcinoma (pNEC).

**Aim(s):** Report patients (pts) with evolution from G1/G2 pNET to G3 pNET or pNEC.

**Materials and methods:** All pts with initial G1/G2 pNET with new biopsy at the time of radiological or clinical progression (within 6 months) were included in this monocentric retrospective study.

**Results:** 13 pts, median age 60 years (45-76) were included. At diagnosis, pNET were localized or metastatic in 3 and 10 pts, and were classified G1 or G2 in 2 and 11 pts, respectively. Median Ki67 was 6% (2%-10%). Before progression, 11/13 pts had received ≥2 different systemic and/or locoregional treatments (excluding surgery). Among these 11 patients, all had received at least one alkylating agent: temozolomide (n=7), streptozotocin (n=1) or both successively (n=3). A new biopsy was performed after a median follow-up of 5 years (1-14), and showed well-differentiated G3 pNET (n=7), pNEC (n=4) or both components (n=2), with a median Ki67 of 50% (22%-85%). 5 pts received VP16-platinum without morphological response. 9 pts received FOLFOX or FOLFIRI with/without bevacizumab, including 5 objective responses among 8 assessable pts. 6 pts died and the median overall survival was 1.5 years (0.1-4) after the new biopsy.

**Conclusion:** The evolution of a well-differentiated pNET towards G3 pNET or pNEC is possible. In case of unusual clinical/morphological progression, a new biopsy should be performed to guide further treatment.

**Keywords:** dedifferentiation, new biopsy.
Infrastructural Alterations in Insulinoma

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Introduction: Insulinomas are the most frequent functioning pancreatic endocrine tumors. Aim(s): Ultrastructural study of insulinomas. Materials and methods: The material from 38 patients has been studied. The average age was 48.2, M/F -10/28. The average tumor's size was 2cm (0.8 to 5.5). G1 tumors were in 95% cases, G2-5%, G3 wasn't present. All tumors were clinical benign. Results: Granules of proinsulin and insulin were present in all β-tumor cells. Two main β-cell phenotypes were: "the light cells", which were dominated by the processes of synthesis of granules and "the dark cells", in which the processes of hormone secretion outside the cell membrane were actively running. The two cell types were connected by the desmosomal junctions. In the area of contact of adjacent cells' cytomembrane the portions of the cytoplasmic fusion with the formation of cytoplasmic bridges were determined. This resulted in the formation of syncytium-like structures. These changes were more common between "the light cells". Through the cytoplasmic bridges the metabolic processes of nutrients and secretory material occurred. Syncytium-like structure due to the large size cannot penetrate through the fenestrated capillary, eliminating the possibility of the formation of the secondary tumors. Moreover, their production makes it impossible to complete the next cell division. Progression of the tumor stops. Conclusion: The formation of syncytium-like structures may be one of the causes of a conservation of a benign potential in insulinoma. Keywords: insulinoma syncytium ultrastructure
Histological Differentiation Provides Useful, Additive and Independent Prognostic Information to Proliferation Index in G2 and G3 Gastroenteropancreatic Neuroendocrine Neoplasms (GEP-NENs)

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Introduction: The WHO 2010 classification has provided a valuable tool to stratify NEN prognosis based on an objective measure, the proliferation index. However, morphology and, in particular, tumor differentiation, is emerging again as a relevant feature that should not be dismissed due to its important clinical implications. Aim(s): To assess the prognostic impact of histological differentiation within WHO 2010 G1/G2/G3 categories. Materials and methods: 1456 out of 2906 patients with GEP-NENs registered in RGETNE met eligibility criteria and were analyzed. Eligible cases must had been typified both by the proliferative index (Ki-67 <3%, 3-20%, > 20%), and by histological differentiation (well differentiated tumors - NETs - or poorly differentiated carcinomas - NECs). The Wilcoxon test was used to compare survival data. Results: According to both parameters patients were stratified into 5 cohorts: NET-G1 (n =609), NET-G2 (n =558), NET-G3 (n =25), NEC-G2 (n =18) and NEC-G3 (n =245). 5-year survival rates were higher for the pairwise comparisons: NET G2 (74.7%, CI 95%, 69.9-79.4%) vs. NEC G2 (56.9%, CI 95%, 31.8-81.9%), p=0.001; NET G3 (41.9%, CI 95%, 24.4-73.7%) vs. NEC G3 (24.2%, CI 95%, 17.5-30.8%), p=0.025; and NEC G2 vs. NEC G3 (as previously shown, p=0.071). Conclusion: Tumor morphology is a relevant aid to further stratify prognosis of patients with GEP-NENs; indeed, histological differentiation provides useful, additive and independent prognostic information beyond proliferation index that should not be dismissed. Keywords: who 2010 classification
High-Grade Gastroenteropancreatic Neuroendocrine Tumors Compare to Neuroendocrine Carcinomas in 276 Patients

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Introduction: The data compared well differentiated high-grade tumors with poorly differentiated neuroendocrine carcinoma (NEC) are very limited. Aim(s): It’s important to differentiate them in pathologic and clinical features. Materials and methods: A total of 276 diagnosed high-grade GEP-NEN were reclassified. 73 cases were reclassified as well-differentiated NET, 203 cases were poorly-differentiated NEC. The clinicopathologic features and survival were analyzed. Results: The mean patient age was similar in High-Grade NET group and NEC group (59.3y vs. 60.9y), and the male/female ratio was 2.65 and 3.23, respectively. The most common sites of High-Grade NETs were stomach (45.2%), pancreas (17.8%), esophagus (9.6%). However, in the NEC group, the most common sites were different, stomach (48.3%), esophagus (20.7%), colon (6.4%). Pancreas NEC was rare, just 3.9%. Lymph node metastasis in High-Grade NET group and NEC group was 35.6% vs. 41.9% (p=0.35). Distant metastasis was obviously different in High-Grade NET group and NEC group (15.1% vs. 29.6%; p=0.019). Patients given platinum-based chemotherapy in High-Grade NET group had a lower response rate than NEC group (26.1% vs. 41.8%, p<0.001). High-Grade NET patients had better survival than NEC patients, the median survival time was significantly different (26m vs. 10m; p=0.009). Conclusion: The High-Grade NET shows different clinical features with NEC. NEC patients had more distant metastasis, and worse survival than High-Grade NET patients. Keywords: well and poorly differentiated, gep-nen, nec, high grade.
A Better Ki-67 Index Cutoff to Redefine Low Grade NET and High Grade NEC in Grade 3 Gastroenteropancreatic Neuroendocrine Neoplasms

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Introduction: Heterogeneity of Grade 3 (G3) gastroenteropancreatic neuroendocrine neoplasms (GEP-NENs) was reported and well-differentiated G3 NET (neuroendocrine tumor) was classified by previous studies. Aim(s): To evaluate the role of Ki-67 index in the heterogeneity assessment of G3 patients and to identify prognostic factors for G3 patients. Materials and methods: Clinical data of 223 patients with G3 GEP-NENs presenting to the Wuhan Union Hospital and the First Affiliated Hospital of Sun Yat-Sen University from 2009 to 2015 was analyzed. Results: Of 223 patients, the median age at diagnosis was 57 years. The most common primary tumor site was stomach. Based on survival analyses, the decision tree analysis revealed Ki-67 index of 45% was the best cutoff to distinguish low grade G3 (Ki-67: 20-45%) from high grade G3 (Ki-67: 45-100%). The total of 60 patients (26.9%) was low grade G3, and 163 patients (73.1%) were high grade G3. Median survival for patients with high grade G3 was 12 months, and for patients with low grade G3 was 22 months. Metastasis (P<0.01) and high grade G3 (P<0.05) were identified as independent prognostic factors for survival and major event-free survival for G3 patients by Cox regression analysis. Conclusion: Low grade G3 and high grade G3 are characterized by significant difference in prognosis. Ki-67 index cutoff of 45% may be a better cutoff to define low grade G3 and high grade G3. Keywords: gastroenteropancreatic neuroendocrine neoplasms, ki67 index, prognostic factors
(G18)
Staging Classification Comparison of Resected Pancreatic Neuroendocrine Tumors (pNETs) Utilizing the National Cancer Database (NCDB)

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Introduction: The staging classification of pNETs remains a matter of debate and no obvious superior system has emerged. Aim(s): To compare 3 current pNET staging classifications using NCDB data from 2004-2014 in patients (pts) who have undergone resection. Materials and methods: Pts with pathologically confirmed pNET, complete data allowing restaging by AJCC (7th ed), ENETS, and mENETS classifications, who had resection of the primary tumor were included (N=4072). Overall survival (OS) was analyzed utilizing Kaplan-Meier curves, log-rank tests were used to compare stage systems. Cox proportional hazards methods were used to control for age, sex, grade, tumor location, functional status, stage, and year of diagnosis. Results: Pts were distributed across stage systems as follows: AJCC: I=55%; II=23%; III=1%; IV=20%; ENETS: I:28%; II:38%; III:13%; IV:20%; mENETS: I:51%; II:23%; III:7%; IV:50%. When AJCC, ENETS and mENETS stage groups were compared, no significant differences were observed for stages I (p=0.9691), III p= 0.6448, and IV (p=1.0). For stage II the 3 stage systems differed (p= <.0001), and mENETS performed better than ENETS due to overlap between ENETS stage I and II (ENETS: HR=1.2, p=0.23; mENETS: HR: 1.85, p<0.0001). Age <60 at diagnosis, female, tumor location at the body and tail, year of diagnosis ≥ 2009, earlier stage, and low grade were favorable prognostic factors Conclusion: AJCC, ENETS and mENETS classifications only differ for stage II pts who undergo primary pNET resection Keywords: pancreatic nets, ncdb, survival, staging, enets
The Positive Expression of PD-L1/PD-1 in Gastroenteropancreatic Neuroendocrine Neoplasias Correlates with Prognosis

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Introduction: The incidence of Neuroendocrine Neoplasias (NENs) is increasing and their pathological characteristics, varied between races. However, the epidemiology of GEP-NENs in Chinese patients remains poorly characterized especially for the expression of important immune checkpoint protein PD1 and PD-L1. Aim(s): This study aims to examine the pathological/clinical characteristics, detect the expression of programmed cell death ligand 1 (PD-L1) / programmed cell death protein 1 (PD-1) in the tissue from patients with GEP-NENs, and analyze the correlation with prognosis furtherly. Materials and methods: Immunohistochemistry staining of PD-1 and PD-L1 was performed in 120 GEP-NENs tissue specimens. Other clinical, pathological data were collected as well. The correlation between PD-1/PD-L1 expression and the prognosis of patients were analyzed furtherly. Results: Immunohistochemical staining indicated that PD-L1 was expressed in the tumor cells of 52.5% patients of GEP-NENs and PD-1 was expressed in tumor infiltrating lymphocytes in 55.8% tumor samples. Meanwhile, survival analysis indicated that the median overall survival (mOS) of patients with PD-L1/PD-1-positive tumors significantly differed from that of patients with PD-L1/PD-1-negative tumors. Conclusion: Our findings indicate that the expression of PD-L1 and PD-1 in the tumor tissue of patients with GEP-NENs are significantly correlated with patient prognosis. Keywords: gastroenteropancreatic neuroendocrine neoplasias, pd-l1, pd-1, immunohistochemistry, prognosis
Introduction: Neuroendocrine carcinoma’s (NEC) are diagnosed by a combination of immunohistochemistry (IHC) and morphology according to the 2010 WHO guidelines. Aim(s): to assess the correctness of NEC diagnosis according to WHO 2010 and to validate prognostic value for overall survival.

Materials and methods: patients registered with a large cell extra pulmonary NEC or extra pulmonary NEC not otherwise specified with the Dutch cancer registry between 2008 and 2012 were included. Pathology was reviewed for morphology and IHC. Patients were correctly diagnosed with a NEC if synaptophysin or chromogranin A was more than 50% positive and MIB or mitotic count confirmed G3 tumor. Overall survival was estimated with Kaplan-Meier and log rank. Results: Of 700 patients registered, 608 complete pathology reports were reviewed. Mean age 66.7 years, 58.6% male. Cases were correctly diagnosed with large cell NEC in 36.5% (N=222). This increased from 25.3% in 2008 to 47.3% in 2012 (P=0.002). Other diagnoses: NET 15.3% (N=93), NET grade unknown 20.7% (N=126), small cell carcinoma 5.9% (N=36), and 21.5% (N=131) not confirmed as NET (IHC neg or not reported). Median survival 2.0 years in NET versus 0.2-0.5 years in the other groups (P<0.001). Conclusion: Increasing number of patients are diagnosed correctly with a NEC along WHO2010 standards, which is of utmost importance for prognostic stratification. Keywords: neuroendocrine carcinoma, ihc, morphology, diagnosis, prognosis, who 2010
Biomarkers for Carcinoid Heart Disease

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Introduction: Carcinoid heart disease (CHD) develops in patients with carcinoid syndrome. Currently NT-proBNP (NTP) is suggested as the best current biomarker to screen for CHD and monitor heart failure. A number of other markers have been investigated for heart failure. Aim(s): In this study we have assessed these markers in three cohorts of NET patients to determine how they compared with NTP. Materials and methods: 3 groups of sbNET patients (n=37) were identified: CHD (Group A, n=10), non-functional (Groups B, n=12, normal CgA, 5HIAA, BNP), functional (Group C, n=15, elevated chromogranin A (CgA) & urine 5HIAA, normal BNP). Analysis was performed using NTP, GAL3, ST2, calprotectin and adrenomedullin assays. Statistical analysis was performed with SPSS. Results: Median values for calprotectin were elevated across all three groups. ST2, GAL3 and adrenomedullin were not elevated. The Kruskal–Wallis test across the 3 patient groups was significant for NTP (p=<0.001) but not for ST2, GAL3, adrenomedullin and calprotectin. The Mann-Whitney U-test was significant (p<0.05) between the CHD and both other groups but was not significant (p=0.12) between the functional and non-functional groups. There was significant correlation between GAL3 and calprotectin. Conclusion: The results corroborate the role of NTP in CHD for NET patients. ST2 may play a role in combination with NTP for risk stratification in CHD and heart failure. GAL3 requires further evaluation given its possible role in the development of cardiac fibrosis. Keywords: carcinoid heart disease
(H2)
Evaluation of Faecal Elastase 1 in Symptomatic Patients with Neuroendocrine Tumours

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Introduction: There is limited data on exocrine pancreatic insufficiency in patients on somatostatin analogues (SSA) which affects quality of life in NETs. **Aim(s):** We explored the value of faecal elastase (FE) as a marker of exocrine pancreatic insufficiency in patients with NETs. **Materials and methods:** 39 patients (27 midgut, 5 pancreatic, 7 other) consecutively referred to a gastroenterology NET clinic completed standardised questionnaires regarding symptoms and quality of life (QoL) as part of clinical care. FE was prospectively evaluated to investigate steatorrhoea. **Results:** 69% had grade 1 NETs with the remainder intermediate (G2) or unknown. Median duration of disease was 69 months (range 9-265). 35/39 NETs (90%) had stage IV disease. 32/39 NETs had complete data, 78% (25/32) of which were established on long-acting somatostatin analogue therapy and 81% (26/32) had steatorrhoea. Only 6/32 patients had a low FE, four complaining of steatorrhoea (12.5%). 22/32 patients had steatorrhoea with a normal FE, 77% (17/22) of whom were on SSAs. Sensitivity of FE in detecting steatorrhoea in NET patients was 15.4%. Less than one fifth of patients exhibiting signs of pancreatic insufficiency had an abnormal FE prior to commencing a trial of pancreatic enzyme replacement therapy. **Conclusion:** There appears to be a lack of association between FE and steatorrhoea in patients with NETs. Many patients experienced steatorrhoea on SSA despite normal FE; thus FE should not be used to evaluate pancreatic function in this group. **Keywords:** quality of life, steatorrhoea, diarrhea, sst
The Clinical Significance of Elevated Serum Procalcitonin in Patients with Gastroenteropancreatic Neuroendocrine Neoplasms

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Introduction: Elevated serum procalcitonin (PCT) was reported in some patients with neuroendocrine neoplasms (NEN), but its clinical significance in gastroenteropancreatic NEN (GEP-NEN) was still unknown. Aim(s): To investigate the association between serum PCT and clinicopathological features, and overall survival (OS) in GEP-NEN. Materials and methods: 130 patients with GEP-NEN were included. Serum PCT levels higher than 1.5× the upper limit of normal (≥0.075 ng/ml) were defined as elevated. Logistic regression analysis was used to evaluate the association between PCT levels and clinicopathological features. Kaplan-Meier method and Cox regression were used to study the prognostic significance of serum PCT. Results: Tumor grade was the sole significant factor associated with elevated serum PCT. Serum PCT were elevated in 14.3% of grade 1, 28.0% of grade 2 and 68.9% of grade 3 patients. Serum PCT was significantly higher in grade 3 compared with grade 1 and grade 2 (P<0.001). Patients with elevated serum PCT had significantly worse overall survival (P<0.001). Cox regression adjusting for age, sex, tumor site, grade, tumor stage indicated that elevated serum PCT was an independent prognostic factor (hazard ratio, 2.413, 95%CI, 1.14 - 5.10; P=0.021). Conclusion: Serum PCT is significantly higher in grade 3 GEP-NEN patients. Elevated serum PCT is an independent factor indicating worse survival. Keywords: procalcitonin, neuroendocrine neoplasms, tumor grade, survival
Mismatch Repair (MMR) Protein Expression is Uncommon in Poorly Differentiated Neuroendocrine Carcinoma

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Introduction: Microsatellite instability (MSI) has been reported to occur in a significant proportion of neuroendocrine carcinoma (NEC) and mixed adenoneuroendocrine carcinomas (MANEC) (11 out of 89 cases, Sahnane et al, ERC 2015). It might be predictive of response to immunotherapy. Aim(s): To evaluate MMR protein expression by immunohistochemistry (IHC) in a series of consecutive patients with metastatic NEC. Materials and methods: Fourteen cases of NEC were studied, including 9 gastroenteropancreatic, 2 thoracic, 1 bladder, 1 head-and-neck and 1 from unknown primary. IIHC for MSH2, MSH6, MLH1 and PMS2 was performed on paraffin embedded tissue, prior to therapy and interpreted according to current recommendations. Primaries (n=6) or metastases (n=8) were analyzed. Results: All tumors contained pure or composite NEC, with 1 tumor harboring a well differentiated contingent and 1 tumor classified as MANEC. Median Ki67 was 70% (range 30-95%). Chromogranin A was positive in 73% of cases, synaptophysin was positive in 100% of cases. MSH2, MSH6, MLH1 and PMS2 were positive in all cases examined. There was no immunohistochemical argument in keeping with MSI phenotype in any case. Conclusion: We did not observe any defect in MMR expression in our series of 14 metastatic NEC G3 patients. MANEC rather than NEC G3 is a more likely candidate for MMR defect in the context of neuroendocrine neoplasms. Keywords: neuroendocrine carcinoma, mismatch repair, microsatellite instability
Peripheral Blood Biomarkers of Systemic Inflammation May Be Prognostic in Metastatic Gastroenteropancreatic Neuroendocrine Tumour (GEPNET) Patients Following 177Lu-DOTATATE (LuTate)

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**Introduction:** LuTate is a treatment for well-differentiated NETs with adequate somatostatin receptor expression. Prognostic biomarkers in this population are lacking. Neutrophil-to-lymphocyte ratio (NLR) is prognostic in the majority of solid tumours but is reported to have less value in indolent well-differentiated NETs. **Aim(s):** To investigate the prognostic impact of NLR, lymphocyte-to-monocyte ratio (LMR) and platelet-to-lymphocyte ratio (PLR) in patients (pts) with advanced GEPNET. **Materials and methods:** We identified pts with well-differentiated GEPNETs who received LuTate for progressive disease or refractory hormonal syndrome. The relationship between baseline biomarkers, histological grade and progression free survival (PFS)/overall survival (OS) was analysed using multivariate regression models. Progression was defined as new or enlarging lesions on 68Ga-DOTATATE PET/CT. **Results:** 84 pts (37% G1, 39% G2, 24% unknown; 52% intestinal, 42% pancreas, 6% unknown) had median follow-up 22 mo, median PFS 31 mo. Elevated NLR (≥5.08), LMR (≥4.17) but not PLR predicted worse PFS (NLR HR 2.77, 95%CI 1.19–6.43, p=0.013; LMR HR 2.45, 95%CI 1.19–5.04, p=0.012). On multivariate analysis, NLR (HR 4.035, 95%CI 1.61–10.11, p=0.003) and LMR (HR 2.65 95%CI 1.12–6.29, p=0.027) remained statistically significant. Median OS was not reached. **Conclusion:** NLR and LMR are potential prognostic biomarkers in patients with progressing, advanced GEPNETs undergoing LuTate therapy. Validation in a prospective trial is warranted. **Keywords:** prognostic, biomarker, prrt, lutate
Plasma Protein Fingerprinting for the Diagnosis of Small Intestinal Neuroendocrine Tumors (siNETs)


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Introduction: siNETs are notoriously difficult to diagnose, especially in an early stage. Aim(s): The EXPLAIN study aimed to investigate 92 plasma proteins (PP), previously shown to be cancer related, in an attempt to find new biomarkers for the diagnosis of siNETs. Materials and methods: This non-interventional exploratory study in the Nordic countries analysed 146 patients with siNET from 17 hospitals and 144 age and sex matched controls (all with written consent). Exclusion criteria were previously treated for NET, other malignant diseases, chronic inflammatory disease, kidney or liver failure. Blood samples (4 ml) were obtained at first visit. Samples analysis used the Proseek Multiplex Oncology II assay to measure relative levels of the 92 cancer related SP. Results: In this first interim analysis, patient characteristics were age 65±10 (mean±SD), 56% male, 48% G1/52% G2, 88% N1/65% M1, 22% >3 bowel mov/d, 12% >3 flushes/d. Several PP (>15) showed significant different mean levels (t-test with Satterthwaite correction) compared with controls (examples: ABL1, EGF, IL-6). In a small subgroup (13%) of patients with low CgA at diagnosis (<120% ULN) 2 PP had mean levels >180% x controls (LYN and FADD). Data will be subjected to statistical supervised learning techniques, random forest and support vector machine. Conclusion: In the diagnostic phase of our exploratory biomarker study we have identified several PP meriting further investigations to evaluate their role in improving diagnostic accuracy. Industry sponsored Keywords: net biomarker diagnosis
PD-L1 Expression and Quantitative Assessment of Tumor-Infiltrating T Cell Subsets in Carcinoid Tumors and Large Cell Neuroendocrine Carcinomas of the Lung

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Introduction: Little is known about the expression of PD-L1 and the immune infiltrate in neuroendocrine neoplasms of the lung. Aim(s): To assess the immune environment in pulmonary carcinoids and large-cell neuroendocrine carcinoma (LCNEC) of the lung. Materials and methods: Sixty-five resected lung NE tumors (49 typical carcinoids (TC), 5 atypical carcinoids (AC) and 11 LCNEC) were studied. Automated immunohistochemistry for PD-L1 (clone E1L3N), CD8 (clone SP16) and FoxP3 (clone SP97) was performed on whole tissue sections from formalin fixed paraffin-embedded tumor samples. Densities of CD8+ and FoxP3+ cells were assessed at the invasion margin (InvM) and in the tumor center (TumC) by image analysis using Definiens Developer XD software under the supervision of a pathologist. Results: The density of CD8+ cells was significantly higher in LCNEC than in TC and AC (p=0.02), both at the InvM and TumC. On the contrary, FoxP3+ cells infiltrate did not significantly differ between tumor types. The immune response was highly condensed at the InvM compared to the TumC in all tumor types. PD-L1 expression was negative (<1% in tumor cells and immune cells) in all tumors. No correlation with stage was found (tumor size, lymph node invasion). Conclusion: We observed heterogeneity in T-cell infiltrates, with higher density of CD8+ infiltrates in LCNEC and absence of PD-L1 expression in lung NE tumors. Correlations with whole exome sequencing data will be presented. Keywords: pd-l1, lung, neuroendocrine, immune infiltrate.
A Nomogram Consisted of Routine Biochemical Tests May Increase the Diagnostic Accuracy of Chromogranin A in Detecting Patients with Neuroendocrine Tumors

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Introduction: Serum chromogranin A (CgA) may be falsely increased in patients with renal impairment and systemic inflammation. Aim(s): We aimed to investigate which laboratory parameters are independently associated with increased CgA and to develop a nomogram in order to improve the diagnostic accuracy of CgA in detecting patients with neuroendocrine tumors (NET).

Materials and methods: We included 155 subjects (controls) and 55 treatment naïve patients with NET, with available data on CgA, other laboratory tests, medical history and anthropometric parameters. Nomogram was developed in a form of scoring system, based on z-score obtained from receiver operating curve analysis for each parameter that was independently associated with CgA. Results: CgA was positively associated with erythrocyte sedimentation rate, red cell distribution width, serum creatinin, glucose, urine leukocyte casts and the use of proton pump inhibitors. Overall, CgA level of 189 μg/L had a sensitivity of 56.4% and a specificity of 76.8% in detecting patients with NET (area under the curve 0.656, P<0.001). In patients with a score of <6, CgA level of 150 μg/L had a sensitivity of 68.2% and a specificity of 89.4%, (AUC 0.767, P<0.001). In patients with a score≥6, AUC decreased to 0.534 (P=0.538). Conclusion: CgA should not be used as a biomarker for NET in patients with laboratory signs of inflammation and renal impairment. Adjustment of CgA in these patients may increase its diagnostic accuracy.

Keywords: neuroendocrine tumor, chromogranin a, accuracy, sensitivity, specificity
PD-1, PD-L1 and PD-L2 Expression in Well-Differentiated Small Bowel Gastrointestinal Neuroendocrine Tumours (Wd SB-NETs)

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Introduction: Treatment options for patients with advanced Wd SB-NETs are limited. **Aim(s):** We describe immune cell infiltration in this disease group.

**Materials and methods:** Patients diagnosed with Wd (WHO grade 1-2) SB-NETs, who had provided informed consent for analysis of archival tissue, were eligible. Programmed death-ligand 1 (PD-L1), PD-L2, PD-1 and tumour infiltrating lymphocytes (TILs) were analysed by immunohistochemistry (IHC); PD-L1, PD1 and PD-L2 were also assessed with reverse transcription polymerase chain reaction (RT-PCR).

**Results:** Of 109 patients screened, 62 were eligible: 54.8% male, median age 64 years; stage II 4.8%, III 40.3% and IV 54.8%; 41.9% were “functioning”. In total, 70 and 63 samples were eligible for IHC and RT-PCR analysis, respectively. Analysed samples were grade (G)1 (67.1%) or G2 (32.86%) NETs; median Ki-67 2%; 67.1% primary SB, 32.86% metastatic sites. There was PD-L1 expression within tumour cells and TILs in 12.8% and 24.3% of samples, respectively. PD1 was present in TILs in 22.8% of samples. No IHC expression of PD-L2 was identified. The majority of samples showed significant presence of CD4 (focal 42.86%; moderate 2.86%) and CD8 (focal 92.86%; moderate 4.29%) TILs. IHC findings were confirmed with RT-PCR which demonstrated higher expression of PD-L1 (p-value 0.007) and PD1 (p-value 0.001) in samples with positive compared to negative-IHC, respectively. **Conclusion:** Due to the observed expression of TILs, the role of immune check-point inhibitors may be explored in this setting. **Keywords:** immunotherapy
LRIG1 Was Down-Regulated in Medullary Thyroid Cancer but No Significant Effect of LRIG1 Was Found in RET2B Transgenic Mice and Human Differentiated Thyroid Cancer

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Introduction: There are four main types of thyroid cancer, papillary (PTC), follicular (FTC), medullary (MTC), and anaplastic. In both PTC and MTC, genomic rearrangements and point mutations in the proto-oncogene RET are common. RET encodes a receptor tyrosine kinase that is negatively regulated by leucine-rich repeats and immunoglobulin-like domains-1 (LRIG1). LRIG1 gene status and mRNA and protein expression correlate with patient survival in different types of cancer. Aim(s): The possible effect of LRIG1 expression in thyroid cancer was investigated in a mouse model and two different clinical cohorts. Materials and methods: A transgenic mouse strain which ectopically expresses the human RET2B oncogene was crossed with Lrig1 knock-out mice. In the RET2B-positive offspring, calcitonin levels were measured and the thyroid glands were investigated by histology. Results: At one year of age, no difference in plasma calcitonin levels or thyroid gland histology was found between Lrig1 knock-out and wild type mice. In the clinical cohorts, LRIG1 was down-regulated in MTC compared to FTC and normal tissue, but no survival difference was found with regard to LRIG1 expression. Conclusion: No effects of Lrig1 could be demonstrated in our RET2B thyroid cancer mouse model and no clinically significant correlations were found with regard to LRIG1 expression. However, because LRIG1 was down-regulated in MTC, possible correlations between LRIG1 expression and patient survival could warrant further investigations in larger MTC materials. Keywords: Lrig1, ret, mtc
The Diagnostic and Prognostic Value of Plasma CgA in Nonfunctional Pancreatic Neuroendocrine Neoplasms

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Introduction: Controversies still remain on the diagnostic and prognostic value of CgA. Aim(s): We aim to explore the diagnostic and prognostic value of plasma CgA in nonfunctional pancreatic neuroendocrine neoplasms (NF-PNENs). Materials and methods: From December 2011 to March 2016, 443 blood samples were obtained for the detection of plasma CgA in recruited individuals (including 167 NF-PNENs patients and 99 healthy people). The data of common characteristics, blood biochemical examination and the postoperative follow-up information and recovery processes were all recorded in all the enrollees. Predictive value of CgA on tumor grade and liver metastasis was assessed using the SPSS statistical package. Results: Of the 167 NF-P-NENs patients and 99 healthy individuals, 49.1% were males. The mean age was 50.02 (range from 19 to 81). 36 patients were grade G1, 102 were G2 and 29 were G3. 47 of all the 167 patients had liver metastasis (28.1%). The median size of the primary tumor was 3.14 cm. The mean CgA values of G1, G2 and G3 P-NENs were separately 75.05 μg/l, 120.69 μg/l and 134.04 μg/l (P=0.046). The mean CgA values of P-NENs with LM and without LM were 161.43 μg/l and 95.02 μg/l (P=0.013). The mean CgA values of P-NENs and healthy control were 136.27 μg/l and 42.20 μg/l (P=0.037), respectively. Conclusion: CgA is a very important marker in the diagnosis in patients with NENs. On NF-PNENs, the level of plasma CgA can be used for the prediction of tumor grade and liver metastasis. Keywords: cga, nonfunctional pancreatic neuroendocrine neoplasms, diagnostic, value
The Exploration of the Clinical Value of Plasma CgA in Nonfunctional Gastroenteropancreatic Neuroendocrine Neoplasms

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Introduction: Controversies still remain on the clinical value of CgA. Aim(s): We aim to explore the value of plasma CgA levels for prediction of diagnosis, clinical features, treatment response in NF-GEP-NENs. Materials and methods: From December 2011 to March 2016, 303 NF-GEP-NENs (including 167 NF-PNENs and 136 NF-GE-NENs) patients and 42 other NENs were obtained for the detection of plasma CgA in recruited individuals. The data of common characteristics, blood biochemical examination and the postoperative follow-up information and recovery processes were all recorded in all the enrollees. Predictive value of CgA on clinical features and therapeutic response was assessed using the SPSS statistical package. Results: Of the 303 NF-GEP-NENs and 42 other neuroendocrine neoplasms, 54.20% was males and the mean age was 53.12. The grade distribution was 26.67% G1, 51.59% G2 and 21.74% G3. For those 303 GEP-NENs and 42 other NENs, the median CgA value was 145.19 μg/l and 82.59 μg/l, respectively. The mean CgA values of G1, G2 and G3 was separately 78.14 μg/l, 153.26 μg/l and 191.12 μg/l (P=0.027). In the aspect of treatment response, partial response (PR) accounted for 15.36%, progressive disease (PD) 18.55%, remission 44.06% and stable disease (SD) 12.75%. The mean CgA values for PR, PD, remission and SD was respectively 127.34 μg/l, 272.68 μg/l, 47.02 μg/l and 103.13 μg/l (P=0.022). Conclusion: For diagnostic value, CgA is more sensitive in NF-GEP-NENs than NF-other-NENs. Moreover, CgA levels are also significantly correlated with treatment response. Keywords: cga, nf-gep-nens, clinical value
The Value of Plasma CgA Combined with NSE Performed As the Real-Time Monitor of Clinical Characteristics in Gastroenteropancreatic Neuroendocrine Neoplasms after the Resection of Primary Lesions

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Introduction: Controversies still remain on the clinical value of CgA and NSE. Aim(s): We aim to determine the clinical values of CgA and NSE in NF-GEP-NENs after surgery. Materials and methods: From December 2011 to March 2016 in our center, 108 of all the 303 GEP-NENs patients have underwent the surgical resection of the primary lesion (35.64%). CgA and NSE were tested in each patient. The data of common characteristics, blood biochemical examination and the postoperative follow-up information and recovery processes were all recorded in all the enrollees. Predictive value of CgA and NSE were assessed using the statistical package. Results: The mean age was 49.98±12.24 and 51.85% was males. For all the 108 patients, the mean NSE value of grade G1, G2 and G3 was separately 13.00μg/L, 16.97μg/L and 21.04μg/L (P=0.002). The mean NSE values of NENs with LM and without LM was 20.06μg/L and 13.80μg/L (P<0.001). From the 108 patients with clinic-pathological characteristics, the mean NSE value of NENs with lymph node invasion and without lymph node invasion was 14.03μg/L and 20.18μg/L (P=0.005). On the aspect of CgA evaluation in those patients, the mean value of patients with and without LM was respectively 86.82μg/L and 244.33μg/L (P=0.012). For the NENs with or without lymph node invasion, the mean CgA values was 145.59μg/L and 119.78μg/L (P=0.023). Conclusion: CgA and NSE are important biomarkers in the diagnosis in patients with NENs. The combined monitor of CgA, NSE can be be an excellent pair of biomarkers predicting the prognosis. Keywords: cga, nse, nf-gep-nens
Clinical Correlates of Discrepant Results of Chromogranin A versus Serotonin Markers in Patients with Neuroendocrine Tumors

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Introduction: Neuroendocrine tumors lead to elevated chromogranin A levels and elevated serotonin markers (urinary 5HIAA and platelet serotonin). These markers are employed for diagnosis and monitoring. Aim(s): To determine the clinical correlates of chromogranin A levels discrepant to serotonin markers. Materials and methods: Chromogranin A, urine 5HIAA and platelet serotonin were evaluated in 143 patients with neuroendocrine tumors (grade 1 and 2) and neuroendocrine cancers (grade 3) from 2005 to 2015. Results: Patients with discrepant results in chromogranin A versus serotonin markers were identified. Elevated chromogranin A with normal serotonin markers was associated with higher grade of the tumor and the use of proton pump inhibitors. Elevated serotonin markers and normal chromogranin A was associated with low grade tumors and limited tumor load. Conclusion: Chromogranin A, urine 5HIAA and platelet serotonin have different characteristics in the diagnosis and monitoring of neuroendocrine tumors. These markers should be used complementary. Keywords: neuroendocrine tumors, chromogranin a, urinary 5hiaa, platelet serotonin
Utility of Serum Chromogranin B Compared with Chromogranin A as a Biomarker in Japanese Patients with Pancreatic Neuroendocrine Tumors

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Introduction: Currently, serum chromogranin A (CgA) is used as a biomarker for pancreatic neuroendocrine tumors (pNET); however, oral use of a proton pump inhibitor (PPI) and renal impairment can affect CgA. Aim(s): The utility of chromogranin B (CgB), belonging to the same granin family as CgA, was examined as a biomarker for pNET. Materials and methods: Serum CgB were determined by radioimmunoassay and serum CgA levels by ELISA in patients with pNET (n = 91) and other pancreatic conditions, and in healthy people (n = 104), to assess the relationships with clinical features. Results: According to an analysis of ROC curves of pNET and controls, the AUC was 0.79 for CgB (sensitivity/specificity: 72%/77%), and 0.78 for CgA (sensitivity/specificity: 79%/64%); thus, CgB and CgA have comparable diagnostic accuracy. The number of cases without liver metastases was significantly larger in pNET patients with positive CgB and negative CgA. In addition, CgB was superior to CgA in differentiation of pNET from other pancreatic diseases, and was not affected by oral PPIs or renal impairment. Conclusion: The pNET diagnostic ability of CgB was approximately equal to that of CgA. Hence, CgB may be useful for early diagnosis of tumors even with no liver metastasis; additionally, CgB may have utility as a biomarker for pNET because it is superior to CgA in differentiation of pNET from other pancreatic diseases and is unaffected by oral PPIs or renal impairment. Keywords: pancreatic neuroendocrine tumors, chromogranin a, chromogranin b
24 Hour Urinary 5-Hydroxyindoleacetic Acid (5HIAA) and Vasoactive Intestinal Peptide (VIP) Doubling-Times (DTs) Predict Disease-Specific Mortality (DSM) in Patients with Neuroendocrine Tumors (NETs)

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Introduction: New clinical prognostic tools are needed in order to select patients with NETs that are at higher risk of DSM. Biochemical biomarker DT is used clinically for prognosis prediction in several solid malignancies. Aim(s): To determine whether biomarker DT has prognostic utility in patients with NETs. Materials and methods: Patients with NETs (n=184) were enrolled in a prospective study with comprehensive biochemical analysis. The current analysis included subjects with at least two consecutive measurements of any biochemical biomarker (chromogranin A, 5HIAA, gastrin, glucagon, pancreatic polypeptide and VIP). DTs for each biomarker were calculated among subjects with increasing levels: DT = \[ \frac{\log_{10} \left( \frac{2^{nd\ value}}{1^{st\ value}} \right)}{\log_{10} (2) \times (\text{time interval between tests})} \]. Exact log-rank test was used to assess differences in DSM risk by DT. Results: No differences in DSM rates were found between patients with increasing vs. not-increasing biomarkers levels of 5HIAA and VIP (p>0.1 for both). Among patients with increasing 5HIAA levels (91/173) four died during a median follow-up of 8 [interquartile range, 12] months, with 5HIAA DT <2 years associated with higher DSM risk (p=0.045) compared with longer DT. Among subjects with increasing VIP levels (92/167) two died during a median follow-up of 8 [11] months. VIP DT <2 years was associated with higher risk for DSM (p=0.004). Conclusion: 5HIAA and VIP DTs <2 years are associated with increased DSM risk and can be used as a prognostic measure in NET patients. Keywords: doubling time, biomarker, prognosis
Association between Neuroendocrine Tumors (NETs) Biomarkers and Tumor Burden Based on Total 68Ga-DOTATATE-Avid Tumor Volume (TV) Measurements

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Introduction: No study has yet assessed the utility of biochemical biomarkers for evaluating NET burden using 68Ga-DOTATATE PET/CT. **Aim(s):** To determine which markers are associated with total NET burden. **Materials and methods:** A retrospective analysis of a prospective database of patients with NETs (n=232). Fasting plasma chromogranin A (CgA), neuron-specific enolase (NSE), gastrin, glucagon, vasoactive intestinal peptide (VIP) and pancreatic polypeptide (PP), and 24-hour urinary 5-hydroxyindoleacetic acid (5HIAA) levels were measured. **Results:** Among patients with pancreatic NETs (PNETs, n=112), TV correlated with CgA (r=0.3, p=0.04, Spearman) and NSE levels had a similar trend (r=0.4, p=0.05). In multiple endocrine neoplasia type 1 patients (n=39) TV correlated with glucagon (r=0.5, p=0.02) and PP levels (r=0.5, p=0.049), and among von Hippel-Lindau patients (n=24)-with plasma VIP (r=0.5, p=0.02) and PP levels (r=0.7, p<0.001). In patients with small intestine NET (SINET, n=74) TV correlated with CgA (r=0.5, p=0.004) and 5HIAA levels (r=0.7, p<0.001), with 5HIAA ≥8.1 mg/24h predicting metastases with high positive (82%) and negative (86%) predictive values (p=0.001). TV in patients with NET of unknown primary (n=16) and NET of other primary locations (n=30) correlated with 5HIAA levels (r=0.8, p=0.002 and r=0.7, p=0.02, respectively). **Conclusion:** Our data supports the use of specific NET markers based on the site of the primary NET, and on the presence of a hereditary syndrome. High 5HIAA levels may indicate metastases in SINET. **Keywords:** pet burden
Preoperative Blood Neutrophil-To-Lymphocyte Ratio-Based Nomogram Predicts Lymph Node Metastasis in Patients of Resectable Pancreatic Neuroendocrine Tumors

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Introduction: Neutrophil-to-lymphocyte ratio (NLR) is one of the systemic inflammation markers, which has prognostic values in many types of tumor. However, hardly no research has reported the relationship between NLR and pancreatic neuroendocrine tumors (panNETs). Aim(s): To evaluate the predictive value of the preoperative blood NLR on the clinical outcomes in patients of resectable panNETs. Materials and methods: 95 consecutive cases of panNETs registered between March 2009 and May 2016 underwent pancreatic surgery were included. Results: Increased NLR was related with advanced T stage, lymph node (LN) metastasis and high Ki-67 index (p < 0.05). The Kaplan-Meier curve indicated that the recurrent free survival (RFS) of patients with high NLR (NLR > 1.40, RFS 61.1±4.4 months) was significantly shorter than those of low NLR (NLR ≤ 1.40, RFS 63.8±2.9 month, p < 0.05). In addition, multivariate logistic regression indicated that, along with T stage (HR 11.94; p=0.01) and Ki-67 index (HR 10.38; p=0.02), NLR (HR 6.74; p=0.02) was also an independent prognostic factors for LN metastasis. Furthermore, a nomogram with a combination of these three independent predictors for LN metastasis demonstrated a good discrimination ability with the AUC of 0.93, which was higher than NLR (0.73), T stage (0.81) and Ki-67 index (0.71) alone. Conclusion: The preoperative NLR is a potential predictor for RFS and LN metastasis. Our nomogram highlights the important role of NLR for LN metastasis for resectable panNETs. Keywords: pancreatic neuroendocrine tumors, nlr, lymph node metastasis
Metastatic Pancreatic Neuroendocrine Tumors (pNETs) and Primary Tumor Resection: A NCDB Survival Evaluation

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Introduction: The role of surgical resection of primary and non-primary site tumors in pNETs is still debated. Aim(s): To evaluate the impact of primary tumor and metastasis resection in patients (pts) with metastatic pNET utilizing the NCDB database from 2004-2014. Materials and methods: Pts with pathologically confirmed metastatic pNETs, complete survival data, and were alive >30 days after diagnosis were included (N=2560). Overall survival (OS) was analyzed utilizing Kaplan-Meier curves, and log-rank tests were used for comparison. Cox proportional hazards was performed to control for age, sex, race, grade, insurance, Charlson/Deyo Score, facility type and location, insurance, primary tumor location, tumor functional status, primary site(PSR), non-primary site(NPSR) and metastasis resection(MS), chemotherapy(CHT), radiation(RT), and year of diagnosis. Results: The cohort male to female ratio was 1.27. 839, 699, and 456 pts underwent PSR, NPSR, and MS respectively. The median OS was 34.3 months for the entire cohort (95% CI: 18.5-36.6), 76.6 for resected pancreatic tumors (95% CI: 71.3 – 86.4), and 20.4 for unresected pancreatic tumors (95% CI: 18.5-22.3), log-rank test <0.0001. In a multivariate analysis, low grade, age <60, body and tail location, and PSR, were favorable predictors for mortality. PSR HR 0.33 (p=<0.0001; 95% CI 0.26-0.42). NPSR, MS, CHT and RT were not correlated with prognosis. Conclusion: Patients with metastatic pNET may benefit from primary tumor resection, independently from CT or RT. Keywords: pnet, metastatic, carcinoid, ncdb
Distribution of 68Ga-HA-DOTATATE and 68Ga-DOTATATE in 343 Patients: Not the Same after All

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Introduction: For the detection of neuroendocrine tumors, 68Ga-DOTATATE was developed but its use is restricted. This led to the development of 68Ga-HA-DOTATATE. In the literature, they are described as having comparable distributions. Aim(s): To retrospectively evaluate the distribution of 68Ga-DOTATATE and 68Ga-HA-DOTATATE in an independent patient population. Materials and methods: All 68Ga-DOTATATE and 68Ga-HA-DOTATATE PET scans between 11-2011 and 04-2016 that were acquired 45±10 minutes post-injection were evaluated. The SUVmax and SUVmean was determined for the liver, spleen, kidney, aortic arch, pituitary-, adrenal-, parotid-, and thyroid glands. Independent sample T-testing was used to determine the difference between 68Ga-DOTATATE and 68Ga-HA-DOTATATE in each organ. Results: 110 DOTATATE and 233 HA-DOTATATE PET scans were included in the analyses. SUVmax was significantly higher in the liver (11.8 vs 8.1), spleen (29.0 vs 19.3), kidney (17.9 vs 14.1), adrenal gland (17.4 vs 12.2), thyroid gland (5.5 vs 3.9), and pituitary gland (6.6 vs 4.8) for HA-DOTATATE. No difference was seen in the parotid. In the blood, the SUVmax was higher with DOTATATE (1.7 vs 1.3). The same significant different pattern was observed for SUVpeak. Conclusion: In this series of 343 patients, 68Ga-DOTATATE and 68Ga-HA-DOTATATE have significant different tissue distributions, which contradicts the current literature. This might have implications in PRRT as 177Lu-DOTATATE and 177Lu-HA-DOTATATE could lead to different radiation doses to healthy organs. Keywords: ha-dotatate
Sensitivity of Glucagon-Like Peptide-1 Receptor (GLP1-R) SPECT/CT, PET/CT and MRI for the Localization of Benign Insulinomas: Interim Analysis of a Prospective Imaging Efficacy Study


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Introduction: 40 patients (pat.) with positive whipple trias were enrolled (ClinicalTrials.gov, NCT02127541). Aim(s): The study aim is to compare the detection rate of GLP-1R PET/CT, SPECT/CT and MRI in pat. with suspicion for an insulinoma. We report preliminary results. Materials and methods: A standardized contrast enhanced 3T MRI was performed. Then pat. received SPECT/CT at 4 and 72h p.i. of 111In-DOTA-exendin-4 and a PET/CT 2,5h p.i. of 68Ga-DOTA-exendin-4 in a randomized cross-over order. 3 independent blinded nuclear medicine physicians and radiologists reviewed the scans. Standard of comparison was the histological diagnosis. Results: So far 29 patients have been operated. A benign insulinoma was confirmed in 25 pat., 1 patient had a nesidioblastosis. In 1 patient histology did not confirm an insulinoma. In 2 patients hypoglycemia ceased postoperatively but histology did not confirm an insulinoma or nesidioblastosis. Both patients were excluded from evaluation as the diagnosis is unclear. 2 patients refused surgery. 3 pat. are awaiting surgery. In 5 patients all imaging modalities did not find a lesion and were thus not operated. 1 patient was excluded because MRI showed evidence for malignancy. Pooled analysis of 27 operated pat. revealed significant higher sensitivity of PET/CT in comparison to SPECT/CT & possibly standardized MRI (92%, 71% and 76%). Conclusion: These preliminary data suggest that PET/CT performs better as standardized MRI imaging and SPECT/CT and will be a useful diagnostic tool if CT/MRI fails to localize the insulinoma. Keywords: insulinoma, glp-1r
FDG-PET Is Superior to WHO Grading in Predicting Overall Survival of Patients with Neuroendocrine Tumors: A Prospective Study of 172 Patients

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Introduction: Accurate grading of patients with neuroendocrine tumors (NETs) is essential for risk stratification and optimal choice of therapy. Currently, WHO grading is based on histopathologically assessed degree of tumor proliferation. Aim(s): To assess the prognostic value of FDG-PET imaging for risk stratification of NETs and compare it with WHO grading.

Materials and methods: We conducted a prospective, single-center cohort study evaluating the prognostic value of FDG-PET imaging and compared it to the current WHO grading. Patients (n = 172) of all grades and with histologically confirmed NETs of gastroenteropancreatic or pulmonary origin were enrolled. The primary end point was overall survival (OS). Progression-free survival (PFS) was a secondary end point. Results: Analysis of the whole cohort revealed that a positive FDG-PET was associated with a poorer OS than a negative FDG-PET (Hazard Ratio (HR): 5.6; 95% CI: 3.1 – 10.2; p < 0.001). In WHO grade 1 and 2 patients (n = 146) a positive FDG-PET was the only identifier of high-risk for death (HR: 5.5; 95% CI, 2.8 – 10.7; p < 0.001). In multivariate analysis, entering FDG-PET and WHO grading, only FDG-PET had independent prognostic value. Conclusion: FDG-PET is useful for risk stratification of all NET grades and is superior to the current WHO grading. FDG-PET could differentiate WHO grade 1 and 2 tumors into low and high-risk groups. In the selection of therapy and for risk stratification of NET patients FDG-PET status should be considered. Keywords: pet, pet/ct, imaging, survival
(I4) 68Ga-NODAGA-exendin-4 PET/CT for the Localization of Insulinomas: Preliminary Data from a Prospective Multicenter Imaging Study


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Introduction: Insulinomas are usually small, single tumors. Precise preoperative localization of the tumor is essential. Imaging techniques like CT and MRI have limited sensitivity and also somatostatin receptor (SSTR) imaging is not specific. Exendin specifically binds the GLP-1 receptor (GLP-1R), which is markedly upregulated in insulinomas. 68Ga-DOTA-exendin-4 PET/CT has been shown to be feasible in detecting insulinomas. Replacing DOTA by NODAGA ensures higher specific activities. We propose 68Ga-NODAGA-exendin-4 PET/CT as a promising new method for improved localization of insulinomas. Aim(s): We present the first cases of a multicenter prospective imaging study to evaluate the effectiveness of 68Ga-NODAGA-exendin-4 PET/CT as a promising new method for improved localization of insulinomas. Materials and methods: 4 adults aged 24-65 with hyperinsulinemic hypoglycemia were included. Standard imaging was performed in all patients, consisting of CT or MRI and SSTR PET imaging. Results: In 1 patient standard imaging as well as GLP-1R PET/CT were negative. Single lesions in the pancreatic body of 2 patients, and 2 lesions in the tail of 1 patient were identified by CT/MRI imaging as well as by SSTR PET/CT. At corresponding locations, GLP-1R positive lesions were clearly visualized using GLP-1R PET/CT, with low background uptake. So far, 2 patients underwent surgery and imaging findings were confirmed. Conclusion: These preliminary results indicate the proof of principle of detecting insulinomas with 68Ga-NODAGA-exendin-4 PET/CT and suggest a valuable role for this new imaging method. Keywords: insulinoma, pet, exendin
Diffusion Weighted Imaging as a Screening Tool in the Detection and Monitoring of Pancreatic Neuroendocrine Tumours in Patients with Familial Cancer Syndromes

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Introduction: Pancreatic neuroendocrine tumours (PNETs) occur at a higher frequency and at a younger age in patients with certain genetic conditions e.g. Von Hippel Lindau and Multiple Endocrine Neoplasia type 1. Screening for early detection and monitoring growth rates of PNETs in these high risk patients is vital in their management. MRI has emerged as the gold standard for imaging the pancreas for the detection of PNETs and diffusion weighted imaging (DWI) has become an invaluable adjunct. Aim(s): We aim to further explore the value of DWI in initial characterisation and in monitoring the tumour growth rate in these high risk groups. Materials and methods: Analysis of our tertiary referral centre identified 61 patients that had MRI pancreas during the last 10 years for indications including screening for VHL, MEN and the investigation of functional PNETs. These images were retrospectively reviewed. Results: 24 patients were identified as having a PNET on MRI. DWI was performed in 15 of the cases. The smallest PNET identified without DWI sequences was 7mm (average size at diagnosis of 24mm) in contrast to 5mm with DWI (average size at diagnosis of 13mm). There were no lesions visible on conventional sequences that were not seen on DWI. Conclusion: We postulate that DWI increases the conspicuity of small PNETs which are often occult on other sequences. We investigate the viability of using a limited MRI examination for screening and surveillance in this high risk patient group. This serves as a pilot for further research. Keywords: pnet, mri, vhl, men1
Value of Somatostatin Receptor Imaging (SRI) in Patients with Appendiceal Neuroendocrine Neoplasms (ANEN) Based on Clinical Follow-Up

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Introduction: Neuroendocrine neoplasms of the appendix are common GEP-NEN tumors. Aim(s): Review the value of Somatostatin Receptor Scintigraphy (SRS) in staging and imaging follow-up of patients with confirmed appendiceal NEN (ANEN) based on clinical follow-up, as single institution experience.

Materials and methods: Overall, 100 patients with confirmed ANEN. SRS using 99mTc Octreotide whole body WB-SPECT/CT as imaging follow-up, disease extent before/after additional surgery were performed in 81 of them.

Results: There were 81 pts with NETG1, 7 pts with NETG2, 10 pts with GCC and 2 pts with MANEC. 31 pts with NETG1/G2 were staged by SRS. There were 4 true positive (TP), 27 true negative (TN), no false positive (FP) or false negative (FN) results (SRS=100% accurate). Furthermore, 40 pts with NETG1/G2 were followed-up by SRS. There were 1 TP, 39 TN, no FP or FN (100% accuracy). In group of GCC and MANEC, 8 pts were staged by SRS. There were 5 TN, 3 FN, no TP or FP. Two pts were followed-up by SRS. There were 2 TN, no TP, FP or FN. Mean time (months) of SRS in most pts after right hemicolectomy was 15 M in staging, 43 M as a follow-up and after appendectomy 22 M as staging and 31 M as follow-up. Conclusion: SRS is highly accurate 100% for staging/follow-up in NETG1/2. It does not detect residual disease in GCC/MANEC. Indeed, it was always negative indicating that SRS had no apparent value as imaging evaluation method before further therapy approach. Keywords: neuroendocrine neoplasm, appendiceal neuroendocrine neoplasm, somatostatin receptor scintigraphy
Ultrasonography Characteristics of Hepatic Neuroendocrine Neoplasm

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Introduction: The incidence of hepatic neuroendocrine neoplasm (HNEN) is significantly increased in recent years. Lack of recognition usually lead to misdiagnosis. Aim(s): To analyze the features of HNEN with ultrasound.

Materials and methods: 50 patients with 54 lesions pathological or eikonic proven HNEN underwent baseline ultrasound (BUS) and contrast-enhanced ultrasound (CEUS). Ultrasonography features of HNEN, distinctions between primary lesions (PHNEN) and metastatic lesions (MHNEN), discrepancies among different pathological grades and primary focus were investigated.

Results: BUS revealed 48.2% (26/54) HNEN appeared hyper-echogenicity, 46.3% (25/54) marginated vaguely. 22.2% (12/54) surrounded by acoustic halo. CEUS disclosed that majority of HNEN washed in hyper-enhancement at arterial phase and wash-out hypo-enhancement rapidly. Average time for HNEN began to enhance, washed out iso-enhancement and hypo-enhancement was 15.6s, 32.1s, 56.3s, respectively. 75.5% (37/49) washed out hypo-enhancement within 60s. 18.5% (10/54) presented capsule enhancement encircling lesions. MHNEN were smaller than PHNEN (3.8cm VS 12.8cm, \(P=0.004\)), and less likely to appear cystic structure (\(P=0.012\)). Distinctions of lesions from different pathological grades or primary focus were not statistically significant (\(P>0.05\), \(P>0.05\)).

Conclusion: Ultrasound revealed the characteristic of HNEN and play an important role in HNEN’s diagnosis, but could identify neither the pathological grades nor primary focus. Keywords: neuroendocrine neoplasm, baseline ultrasound, contrast-enhanced ultrasound, hepatic
Application of Parametric Contrast-Enhanced Ultrasound for Early Treatment Response Evaluation in Metastatic Hepatic Neuroendocrine Neoplasm

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Introduction: Since shrinkage of lesions in patients with metastatic hepatic neuroendocrine neoplasm (MHNEN) receiving systemic therapy is rarely observed, limit of RECIST for evaluating treatment response gradually emerged. Aim(s): To investigate the feasibility of parametric contrast-enhanced ultrasound (CEUS) for early therapeutic response evaluation.

Materials and methods: 13 MHNEN patients who received systemic therapy underwent baseline ultrasound, 2D-CEUS and 3D-CEUS pre-treatment and post-treatment regularly (after 1/2, 1, 2 and 3 period of treatment). CEUS raw data was analyzed to render time-intensity curve and extract parameters: peak intensity (PI), area under curve (AUC) and slope. Treatment response was assessed with CECT according to RECIST. Relation between percentage of parameters changed (Δparameter%) and response, distinction between 2D and 3D-CEUS were analyzed.

Results: For 2D-CEUS, ΔAUC(%) after 1/2 period and Δslope(%) at the end of protocol reduced in effective group (n=10) while rose in ineffective group (n=3) (P=0.017, P=0.011). For 3D-CEUS, ΔPI(%), ΔAUC(%) after 1/2 period, ΔPI(%) after 1 period and ΔPI(%), ΔAUC(%) at the end of protocol reduced in effective group, while rose in ineffective group (P=0.030, P=0.017, P=0.011, P=0.018, P=0.028, P=0.011). 3D-CEUS contained more parameters to reflect therapeutic effect than 2D-CEUS.

Conclusion: Parametric CEUS can be used for early treatment response evaluation in MHNEN patients, 3D-CEUS is more sensitive than 2D-CEUS.

Keywords: neuroendocrine neoplasm, hepatic, parametric ceus, early response evaluation
Safety and Tolerability of "Ready-to-Use" (SOMAKIT TOC®) 68Ga-DOTA0-Tyr3-Octreotide (68Ga-DOTATOC) for Injection in Patients with Proven Gastro-Entero-Pancreatic Neuroendocrine Tumours (GEP-NETs)

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Introduction: 68Ga-DOTATOC (PET) has superior diagnostic performance than Octreoscan (SPECT) in patients with GEP-NETs. Aim(s): A new “ready-to-use” 68Ga-DOTATOC formulation for injection aims to simplify the synthesis of the final radiotracer. Materials and methods: This phase I/II multicentre, open label study assessed the safety and tolerability of a single dose of 68Ga-DOTATOC (prepared on the day of the scan; product stability: 4 hours) 2 MBq/kg ± 10% (range 100-200 MBq) in patients with biopsy-proven grade 1-2 GEP-NETs. PET-CT imaging was performed 40-60 minutes post injection. Patients were followed-up for 28 days for safety/ tolerability assessment. Results: Twenty consenting patients; 14 males, 6 females; mean age 58 years (41–84 years); ECOG performance status 0 (75%) and 1 (25%); mean BMI of 26.4 Kg/m²; G1 70%, G2 30%; and 75% with stage IV disease were recruited; all were evaluable. The mean 68Ga-DOTATOC activity injected per patient was 162.37 MBq (standard deviation (SD) 26.04). The mean time of PET/CT scan was 58 min (SD 12) post injection. Twelve patients experienced at least one adverse event (AE) during the study; 27 AEs were reported (85% grade 1; 15% grade 2), none serious; no grade 3-4 toxicities. Only 4 AEs were classified as possibly (headache (n=1; 4%), nausea (1; 4%)) or probably (dysgeusia (1; 4%), paraesthesia (1; 4%)) related to the study preparation. Conclusion: The “ready-to-use” preparation of 68Ga-DOTATOC for injection was safe and well tolerated. Keywords: somakit, dotatoc, gep-net
Endoscopic Ultrasound Appearance of Pancreatic Serotonin-Staining Neuroendocrine Neoplasms: A Case Series

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Introduction: The pancreatic localization of serotonin-staining neuroendocrine neoplasms (serotoninomas) is extremely rare. Less than 350 cases have been reported in the world literature. Aim(s): To describe a small series of 8 pancreatic serotoninomas in order to analyze the endoscopic ultrasound (EUS) appearance of this rare type of pancreatic neuroendocrine neoplasm (pNEN). Materials and methods: Between 2010 and 2016, all consecutive patients with histologically proven pancreatic serotoninoma who had undergone EUS were enrolled. Results: 8 patients (6F, median age 68.5 yrs) had a diagnosis of pancreatic serotoninoma and underwent EUS examinations. Three had a G2 NEN, 5 had G1. Two patients had metastatic disease. Median diameter of the lesion was 10 mm. The nodule echotexture was hypoechoic in 7/8 cases. The most frequent localization was the pancreatic neck (4); in 3 cases, the tumor was located in the pancreatic head and in one in the body. In 7 cases the tumor caused a main pancreatic duct dilation; in 3 cases also the secondary ducts were dilated. In one case a dilation of the common bile duct was observed. At contrast-enhanced EUS (CE-EUS) no one showed the typical contrast-enhancement. Elastography (available in 2 patients) showed a rigid pattern of the lesion. One patient showed a full-blown carcinoid syndrome Conclusion: From this case series a specific EUS appearance resulted for pancreatic serotoninoma, different from other types of pNEN. It appears difficult to differentiate it from both IPMN and pancreatic adenocarcinoma. Keywords: pnen
68Ga-DOTA-TOC and 18F-FDG-PET/CT in the Follow-up of NET Patients Treated with First Full PRRT

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Introduction: Only few studies have correlated 18F-FDG and SSTR imaging with NET grade. Aim(s): Compare 68Ga-DOTA-TOC and 18F-FDG-PET/CT in follow-up of NETs treated with PRRT. Materials and methods: 66 patients with proven NET that underwent PRRT and 3 combined 68Ga-DOTA-TOC and 18F-FDG-PET/CT were evaluated. PET was performed before PRRT, 3 months after completion of PRRT and 6-9 months thereafter. Results: 62/198 (31%) 18F-FDG-PET were true-positive in 38/66 (58%) patients. 28 patients (G1,5; G2,23 patients) were 18F-FDG-negative initially and during follow-up, 24 patients (G1,5; G2,13; G3,6 patients) were 18F-FDG-positive initially and during follow-up, 9 patients (G1,2; G2,6; G3,1 patient) were initially 18F-FDG-negative, but converted to 18F-FDG-positive during follow-up, and 5 patients (all G2) were initially 18F-FDG-positive, but converted to 18F-FDG-negative during follow-up. 18F-FDG-PET showed more and/or larger metastases than 68Ga-DOTA-TOC-PET in 5 patients, all with progressive disease. In 3 patients with progressive disease SUVmax of tumors increased 41-82\% from first to last investigation. Conclusion: 18F-FDG-positive tumors correlate with higher risk of progression in NETs. Initially 18F-FDG-negative NET patients may show 18F-FDG-positive tumors during follow-up. G1 and G2 NET patients may have 18F-FDG-positive tumors. 18F-FDG-PET/CT is a complementary tool to 68Ga-DOTA-TOC-PET/CT with clinical relevance in the follow-up and for assessment of prognosis in NET patients. Keywords: 68ga-pet, fdg
Introduction: 18F-FDG-PET is widely used to detect malignant tumors. However, the efficacy for pancreatic neuroendocrine tumors (PNETs) is reported to be limited in the clinical practice. Aim(s): In this study, we reassessed the clinical significance of detection of PNET by 18F-FDG-PET. Materials and methods: We retrospectively reviewed patients with PNETs who were treated at Kyoto University Hospital between January 2007 and December 2016. Patient’s backgrounds, clinical course and imaging were collected from the medical records. We compared the findings of images, including 18F-FDG-PET, between patients with or without metastatic diseases. Results: Eighty patients (G1:G2:G3=52:26:2) were diagnosed as PNET and treated at our department. In G1 group, 4 patients (8%) with non-functioning PNETs experienced liver metastasis (synchronous: metachronal=3:1). In ≥G2, 15 patients (53%) experienced liver metastasis (synchronous: metachronal=8:7). The sensitivity and specificity rate of 18F-FDG-PET were 67% (2/3) and 73% (35/48) in G1, whereas 71% (10/14) and 85% (22/26) in ≥G2. The positive/negative predictive value was 13%/95% in G1, whereas 71%/85% in ≥G2, respectively, indicating metastatic PNETs were highly positive in 18F-FDG-PET even in G1 group. Conclusion: 18F-FDG-PET provides us information about the possibility of establishing metastatic disease even in patients with proliferatively inactive PNETs. We might be able to select patients who should be closely followed. Keywords: 18f-fdg-pet, pancreatic neuroendocrine tumors (p-nets), metastasis
Radiological Changes in the Treatment of Pancreatic Neuroendocrine Tumors (PNET) with Sunitinib: RECIST vs CHOI Criteria. CRIPNET-GETNE Study

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Introduction: In PNET, phase III studies with antitarget drugs show few responses based on RECIST criteria despite a significant impact on progression free survival (PFS). Antiangiogenic drugs show in other tumors that responses are not always associated with a reduction in tumor volume on CT. Aim(s): To explore CHOI vs RECIST criteria. Materials and methods: CRIPNET-GETNE study include patients with advanced unresectable PNET treated with sunitinib who were evaluated by Computed Tomography (CT) using CHOI and RECIST criteria, every 3 months until progression (PD). Choi criteria sets partial response (PR) as a decrease in size of ≥10% or a decrease in tumour density (Hounfield Units, HU) ≥15% on CT. RECIST criteria sets PR as a decrease in size of ≥30% of the sum of diameters. Results: 65 patients were recruited between 2008 and 2016. We present imaging data of 21 patients. At the time of analysis, 81% patients presented PD. 90% showed a radiological response by CHOI criteria versus 33% by RECIST. The median PFS was 18.03 months: 18.03 months (95%CI, 16.32-22.7, p 0.412) in patients with CHOI response and 15.43 months (95%CI, 13.89-16.97 p 0.582) in those with RECIST response. Choi criteria yielded a PFS of 4.87 months in non-responders vs 18.03 months in responders, p 0.412. Conclusion: CHOI criteria seem to be more accurate than RECIST in advanced PNET treated with sunitinib. Matured and expanded data will be presented at the congress. Keywords: sunitinib, pnet, choi, recist

Neuroendocrinology 2017;105(suppl 1): 1-338
Should the Selective Arterial Secretagogue Injection Test for Insulinoma Localization be Evaluated at 60 Seconds or at 120 Seconds?

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**Introduction:** The selective arterial secretagogue injection (SASI) test is considered indispensable for an accurate insulinoma localization. The optimal timing of post-injection evaluation has not been established yet, as some studies recommend 60 seconds [SASI (60 sec)] while others support 120 seconds [SASI (120 sec)]. **Aim(s):** To determine the optimal timing for SASI test evaluation for insulinoma localization. **Materials and methods:** Thirteen patients with surgically proven insulinoma were studied retrospectively. For the SASI test, immunoreactive insulin (IRI) was determined at baseline, and after 30, 60, 90, and 120 seconds after calcium gluconate injected. The localization detection ability of SASI (60 sec) and SASI (120 sec) was compared. **Results:** In 13 patients, a secretagogue was injected into 40 arteries supplying the pancreas. In the SASI (60 sec) and SASI (120 sec), the respective findings were as follows: positive predictive value, 72.2% and 68.2%; false positive rate, 25.0% and 35.0%; and rate of positive in both head and body/tail, 38.5% and 46.2%. The localization detection sensitivity was 76.9% for SASI (60 sec) and 92.3% for SASI (120 sec). The sensitivity of morphological imaging techniques for localization was 61.5–91.7%. **Conclusion:** Compared with SASI (60 sec) or morphological imaging, the insulinoma localization detection ability of SASI (120 sec) was superior. Therefore, the IRI level should be measured until 120 seconds in the SASI test. **Keywords:** insulinoma, selective arterial secretagogue injection test, localization, insulin
Triple Tracer Imaging Approach for the Non-Invasive Assessment of Chemokine Receptor 4 Expression in Gastroenteropancreatic Neuroendocrine Tumors


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Introduction: The theranotic twins [68Ga]Pentixafor and [177Lu]Pentixather for chemokine-directed endoradiotherapy (ERT) were recently developed. Aim(s): We aimed to evaluate feasibility of non-invasive CXCR4 PET/CT imaging using [68Ga]Pentixafor in comparison to 68Ga-DOTA-D-Phe-Tyr3-octreotide ([68Ga]DOTATOC) and 18F-fluorodeoxyglucose ([18F]FDG).

Materials and methods: 12 patients with histologically proven GEP-NET underwent [68Ga]DOTATOC, [18F]FDG and [68Ga]Pentixafor PET/CT. Scans were analyzed on a patient as well as on a lesion basis. Results: All G1 NET (n=3) were [68Ga]DOTATOC-positive and [68Ga]Pentixafor-negative; [18F]FDG-PET yielded positive results in 2/3 patients. [68Ga]DOTATOC was the superior tracer in all cases. All G2 NET (n=4) were both SSTR- and [18F]FDG-positive, whereas CXCR4-positivity could only be observed in half of the cases (2/4). [68Ga]Pentixafor did not yield additional information in any G1 or G2 NET. Investigating G3 NET, 5/5 subjects were rated [18F]FDG positive. CXCR4- and SSTR-PET identified lesions in 4/5 patients each. Of note, the majority of the [68Ga]Pentixafor-positive subjects presented with Ki67 of ≥85%, whereas well-differentiated tumors did not demonstrate relevant CXCR4 receptor expression. Conclusion: Increasing chemokine receptor expression could be non-invasively observed in terms of dedifferentiation. CXCR4-directed ERT can be envisioned for selected patients demonstrating increasing malignancy or [68Ga]DOTATOC negative findings.

Keywords: neuroendocrine tumor, [68Ga]pentixafor, cxc4, prrt, pet/ct
Introduction: 18FDG-PET/CT was the most widely used functional imaging for cancer, while 68Ga-DOTA-TATE PET/CT could evaluate the SSTR expression of NEN. Aim(s): This study aimed to assess the value of 18FDG and 68Ga-DOTA-TATE PET/CT in Gi-NEN patients and illustrate the correlation between glucose metabolism, SSTR expression and differentiation of tumor. Materials and methods: 36 patients (27 males, 9 females, age: 27-77 years) with definite histological diagnosis of Gi-NEN who underwent 18FDG and 68Ga-DOTA-TATE PET/CT in two weeks were involved in this retrospective study. All the patients had primary lesions or metastases. G/F= (68Ga-SUVmaxlesion/68Ga-SUVmax normal liver) / (18F-SUVmaxlesion/18F-SUVmax normal liver) Results: The positive rate of 18FDG and 68Ga-DOTA-TATE PET/CT in different grade of Gi-NEN was 37.3% and 50% (G1, 3/8 and 4/8), 58.3% and 75% (G2, 7/12 and 9/12) and 100% and 31.3% (G3,16 /16 and 5/16) respectively. Means of SUVmax in these three groups were 3.9, 4.16, 12.05 in 18FDG and 37.1, 20.71, 10.49 in 68Ga-DOTA-TATE. 18F-SUVmax presented positive correlation with Ki67 (r=0.693, P=0.000), on the contrary, there was negative correlation between 68Ga-SUVmax, G/F and Ki67(r=0.544, P=0.002; r=0.679, P=0.000). Conclusion: Glucose metabolism and SSTR expression were both correlated with differentiation of Gi-NEN. These two imagings showed different biological characteristics for clinical diagnosis and therapy, and played complementary role to Ki67 value. Keywords: 18fdg, gastrointestinal, neuroendocrine, neoplasm, standard, uptake, value
A Comparison of 68Ga-DOTA-TATE and 18F-FDG PET/CT Imaging on Patients with Pancreatic Neuroendocrine Neoplasm (pNEN)

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Introduction: 68Ga-DOTA-TATE and 18F-FDG PET/CT are widely used for staging patients with pNEN. The sensitivity of nuclear modalities with pathologic correlation is unknown. Aim(s): To evaluate the efficacy of both DOTATATE and FDG PET imaging on patients with pNEN. Materials and methods: From June 2012 to April 2016, 17 patients with histologically-confirmed pNEN who both performed nuclear imaging were identified. The interval between the two imaging was less than 2 weeks. Results: In the cohort, 6 males and 11 females, 10 (58.8%) NET and 7 (41.2%) NEC with a median age of 53 years (38-75). 15 cases had distant metastases, with liver (70.6%) as the most common site. Sensitivity of DOTATATE and FDG PET was similar (76.5% vs 64.7%; p=0.7). The SUVmax of DOTATATE in NET was higher than that in NEC (31.72 vs 23.34, p=0.43), while the the result was inverse as for FDG PET (4.23 vs 9.60, p=0.006). The SUVmax of DOTATATE had no correlation with Ki67 index (R=-0.40, p=0.11); while a positive correlation between SUVmax of FDG PET and Ki67 index was observed (R=0.54, p=0.02). The ratio of lesion-related SUVmax to SUVmean liver of DOTATATE versus FDG PET showed an inverse relationship (R=-0.51, p=0.03). Conclusion: Imaging results of pNEN were correlated with tumor grade and differentiation. DOTATATE appeared more sensitive for NET, whereas FDG PET showed superior sensitivity for NEC. The two nuclear modalities exhibit an indicator of biological behavior of pNEN besides Ki67 index, but the clinical relevance of this finding has to be proven in larger studies. Keywords: pnen, 68ga-dotatate, 18f-fdg-pet
Shear Wave Elastography Imaging in Neuroendocrine Liver Metastases: Preliminary Data from a Single Center

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Introduction: Ultrasound shear wave elastography (SWE) imaging has recently been developed as non-invasive method for quantitative assessment of liver stiffness. Aim(s): Present series was aimed at evaluating the stiffness of neuroendocrine liver metastases by SWE during an ultrasound examination.

Materials and methods: From 2014 to 2016 all consecutive patients attending our Gastroenterology Unit for a metastatic neuroendocrine tumor underwent ten consecutive SWE measurements (ElastPQ ultrasound shear wave elastography) for both the major liver metastasis and the surrounding hepatic parenchyma. Results: In the 15 patients included (9 M, median age 66 yrs, range 52-78), the primary neuroendocrine tumor was located at the pancreas (#5), the small bowel (#9) or unknown (#1). Grading was G1 in six patients, G2 in six and not available in three. The lesions appeared as hyperechoic (#7), hypoechoic (#3), isoechoic (#1) or mixed (#4). The median values of SWE were 10.7 KPa (SD 4.0; range 4.4-55.7) in neuroendocrine liver metastases and 4.7 (SD 1.8; range 3-13.6) in the surrounding liver parenchyma (p<0.01). No correlation was observed between SWE measurements and grading, primary tumor site and liver metastasis size.

Conclusion: According to present data, SWE was significantly higher in neuroendocrine liver metastases than in the surrounding parenchyma. However, the potential role of SWE in the diagnostic work-up of neuroendocrine liver metastases remains to be furtherly investigated.

Keywords: shear wave elastography, neuroendocrine liver metastases

Neuroendocrinology 2017;105(suppl 1): 1-338
The Characteristics and Survivals of Gastrointestinal Neuroendocrine Tumors, A Single Center Experience from Developing Country

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Introduction: Gastrointestinal neuroendocrine tumors (GINETs) are a heterogeneous group of tumors with variable behaviors. We analyzed baseline characteristics and outcomes of GINETs and impact of the tumor grade on the overall survival. Aim(s): To evaluate Characteristics and survivals of gastrointestinal neuroendocrine tumors, at a single center from developing country. Materials and methods: We retrospectively studied baseline characteristics of 85 patients registered at our institute with the diagnosis of GINETs from January 2006 to January 2016. The impact of the tumor grade was seen on the OS. Results: There were 60 (70.6%) males and 25(29.4%) females. The mean age at presentation was 51 years. Grade I, II, III tumors were 61.2%, 11.8%, 27.1%, respectively. The most commonly involved site was pancreas 48.2%. Localized vs. metastatic disease was seen in 68.2% and 31.8%, respectively. 81 patients were sporadic NETs while 4 patients had features of MEN I Syndrome. Asymptomatic, carcinoid syndrome and symptoms related to disease site were seen in 22.4%, 10.6% and 67.1% respectively. The OS was 26.36 months. Patients with grade I, Grade II and III tumors had OS of 36.27, 28.89 and 13.92 months, respectively. Small number of patients received targeted therapies due to cost issues. Conclusion: GINETs are rare tumors with good outcomes in grade I and II, and poor outcome in grade III. Provision of targeted therapies is important from the government agencies for better outcome. Keywords: neuroendocrine tumors, retrospective studies
Effectiveness of Chemotherapy in Advanced PanNETs with ki67<55%: Monocentric Experience

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Introduction: Pancreatic Neuroendocrine Tumors (panNETs) are neoplasms with heterogeneous clinical behaviour. There is no standard treatment. Aim(s): The aim of this study is an evaluation of different chemotherapy regimen in first or subsequent line of treatment in advanced panNET with ki67<55 ("G3 low").

Materials and methods: We retrospectively reviewed data from 45 patients (P) with locally advanced or metastatic pNET treated with chemotherapy during 2011-2016. Mixed histology and ki67> 55% were excluded. 60% P received two drugs (2C) combination (STZ or platinum or TMZ based) and 40% tree drugs (3C) (mFOLFIRINOX or DTIC+CDDP+5FU). We evaluated separately the two groups. According to the WHO classification there were respectively 3.7% and 5.6% G1; 59.3 % and 27.8% G2; 37% and 66.7% “G3 low”. 89.3% of P in the 2C group (48% liver only) and 83.3% in 3C (33.3% liver only) had metastatic disease. Morphological response was assessed according to RECIST1.1 criteria. Results: In the 2C we obtained 85.2 % disease control rate (DCR): 44% (12/27) PR and 40.7% (11/27) SD. In the 3C DCR was 78.6% with PR 64.3% (9/14) and SD 14.3% (2/14). Median PFS (mPFS) was 9 and 5.67 months for 2C and 3C respectively. 6 P (15%) underwent surgery with radical intent; they were equally distributed in both groups. Conclusion: This study has demonstrated activity of 2C and 3C treatments in panNETs and the effectiveness also in neoadjuvant setting. Keywords: chemotherapy, neuroendocrine, pan nets, ki67<55%
FOLFIRI Regimen with or without Bevacizumab as Second-Line Therapy Showed Activity in Patients with Metastatic Gastroenteropancreatic Neuroendocrine Carcinoma

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Introduction: Metastatic disease of GEP-NEC is tough condition in clinical practice. And the role of the second-line therapy remains unknown. Aim(s): To explore efficacy and safety of FOLFIRI ± BEV in 2nd treatment.

Materials and methods: Eleven GEP-NEC patients were treated with FOLFIRI regimen ± BEV after failure of first-line chemotherapy between July 2014 and June 2016 in our center. Data including clinical and pathological parameters were collected at the time of diagnosis and during treatment. Results: 11 patients enrolled in this study. Median ECOG score was 1. Most were male (81.8%). Half of patients were pancreatic NEC (6pts, 54.5%). Metastatic disease was evident at diagnosis in all patients. The median Ki-67 index was 80%. 8 of all patients (n=11) received EP regimen as first line chemotherapy, 3 patients who experienced other regimens. All patients received FOLFIRI with a median number of 8 (3-36) courses. 3 patients (27.3%) had PR, 4 (36.4%) SD, and 4 (36.4%) PD. But in 6 patients received the FOLFIRI plus BEV, DCR was 66.7%, 3 (50.0%) PR, 1(16.7%) SD. The median PFS in all 11 patients was 3.77 months, 6 patients with BEV was 4.77 months. The median OS in all 11 patients was 6.30 months; 6 patients with BEV was 7.2 months. The most common observed severe toxicity was grade 3 neutropenia, other adverse effects were mild to moderate.

Conclusion: FOLFIRI regimen was an effective tx and well tolerated in 2nd therapy NEC. Additional anti-VEGF therapy with BEV may improve disease control and prolong survival time.

Keywords: nec, folfiri, bevacizumab
5-Fluorouracile Plus Dacarbazine in Metastatic Digestive Neuroendocrine Tumors: Efficacy and Potential Biomarkers

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Introduction: The 5-fluorouracile (5FU) + dacarbazine (DTIC) combination has been poorly evaluated in NET Aim(s): To assess the efficacy and safety of 5FU-DTIC and to explore potential predictive factors of efficacy Materials and methods: Medical and imaging records of all consecutive patients (pts) with metastatic well-differentiated pancreatic (p) or small intestine (si) NET receiving 5FU-DTIC between 2004 and 2015 in 3 expert centres were retrospectively reviewed. Tumor expression of DAXX, ATRX, MGMT and APNG was centrally performed Results: We included 53 pts of median age 61 years (37 pNET and 16 siNET, 13 with functioning syndrome). Median Ki67 was 10% (1-36) and 68% of NET were grade 2. 68% of pts presented at least 2 metastatic sites. 87% of pts had WHO performance status of 0-1. 5FU-DTIC was the first, second or third line of treatment in 13, 20 and 9 pts, respectively. At 5FU-DTIC initiation, 43/43 pNET were progressive. Median duration of 5FU-DTIC duration was 8.4 months. RECIST PR and SD were obtained in 51% and 32% of pNET pts, and in 19% and 63% of siNET pts, and median PFS was 28.7 months (95% CI, 18-38) and 9.4 months (95% CI, 0-38) in the two groups, respectively. Most frequent toxicities were nausea (40%), asthenia (38%) and thrombocytopenia (32%). Only 4 pts had a grade 3 toxicity. 28% of pts had dose reduction Conclusion: 5FU-DTIC was well tolerated and effective, especially in metastatic pNET pts. The predictive impact of DAXX, ATRX, MGMT and APNG will be reported at the meeting Keywords: chemotherapy, tumor response, tolerance, pfs
Chemotherapy for Pulmonary Large Cell Neuroendocrine Carcinomas: Does the Regimen Matter?

Introduction: Metastatic pulmonary large cell neuroendocrine carcinoma (LCNEC) is a rare disease and the most effective chemotherapy regimen is debated, i.e. small cell lung carcinoma (SCLC) or non-small cell lung carcinoma (NSCLC) chemotherapy. **Aim(s):** To analyze chemotherapeutic treatment for LCNEC on a population basis. **Materials and methods:** The Netherlands pathology registry (PALGA) and cancer registry (IKNL) were searched for patients with LCNEC diagnosed between 2003-2012. In 207 patients tumour slides were available for panel-revision. Data on clinical characteristics and chemotherapy were retrieved. First-line platinum combined chemotherapy was clustered: 1) gemcitabine, docetaxel, paclitaxel or vinorelbine as NSCLC type, 2) pemetrexed as pem-NSCLC type, and 3) etoposide as SCLC type. **Results:** 128 of 207 patients had a panel-consensus diagnosis of LCNEC. NSCLC type chemotherapy was administered in 46% (N=60), pem-NSCLC type in 16% (N=20), and SCLC type in 38% (N=48) patients. NSCLC type chemotherapy treated patients had a median overall survival (OS) of 8.5 [95% confidence interval (CI) 7.0-9.9] months, significantly longer than treatment with pem-NSCLC type; median 5.9 [95% CI 5.0-6.9] months (Hazard Ratio (HR)=2.51 [95% CI 1.39-4.52], P=0.002) and SCLC type; median 6.7 [95% CI 5.0-8.5] months (HR=1.66 [1.08-2.56], P=0.020). **Conclusion:** Patients with LCNEC treated with NSCLC type chemotherapy have longer OS compared to pemetrexed NSCLC type and SCLC type chemotherapy. Prospective trials are warranted. **Keywords:** lcnc, chemotherapy, nec, lung

Neuroendocrinology 2017;105(suppl 1): 1-338
Introduction: The choice of first-line treatment of metastatic pancreatic neuroendocrine tumors (mP-NET) is mainly based on prognostic factors. ENETS-2016 guidelines proposed treatments according to 3 groups: Group-1, patients in whom all lesions could be removed; Group-2, patients with Ki67<10%, low tumor burden, no symptoms, and stable disease, for whom a watch-and-wait strategy or somatostatin analogs are proposed; Group-3, symptomatic patients or with Ki67>10% or significant tumor burden or progressive disease, for whom a systemic chemotherapy is proposed. Aim(s): This study aimed to determine distribution, patient characteristics, and outcome among these 3 groups.

Materials and methods: Patients with mP-NET from 2004 to 2016 were categorized into the 3 groups. Prognosis was calculated using the Kaplan-Meier method. All treatments were recorded and consistency with ENETS guidelines was explored.

Results: 104 patients were analyzed, 64% synchronous mP-NET, 80% grade 2 tumors, median overall survival (OS) of 104 (95%CI: 65-143) months. There were 15 patients in ENETS Group 1, 16 in Group 2, and 73 in Group 3. Median OS was not reached in Groups 1-2 and was 64 months (35-93) in Group 3. High liver tumor volume, high-grade tumor, and tumor slope were associated with worse OS in multivariate analysis. The first-line treatment was in accordance with guidelines in 82%, and 57% of deceased patients received less than 4 lines of treatment.

Conclusion: Most patients are in Group-3 and do not receive all available treatments.

Keywords: pancreas, metastasis
Pancreatic NET-G3 Does Not Respond to Platinum-Based Chemotherapy: A Multicenter Study of Neuroendocrine Carcinomas

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Introduction: Recent studies have shown that Pancreatic neuroendocrine carcinomas (NECs) contain well-differentiated NETs with high proliferative activity (WDNET-G3), as well as poorly differentiated NECs (PDNECs). Although patients with pNEC show variable responses to platinum-based chemotherapy, predictors of the response are unknown. Aim(s): The objective was to examine the clinicopathological and molecular features of pNEC and to assess the response to chemotherapy and survival in a multicenter, retrospective analysis. Materials and methods: A total of 100 patients diagnosed with pNEC were enrolled. After the histological review, 70 pNECs were grouped into WDNET-G3 and PDNEC. The clinicopathological and molecular features of WDNET-G3 and PDNEC were characterized. Results: WDNET-G3 was seen in 21 (30\%), while PDNEC in 49 (70\%). The Ki67 labeling index, Rb immunolabeling, KRAS mutation, total chemotherapy response rate (RR), platinum-based chemotherapy RR, and prognosis were significantly different between WDNET-G3 and PDNEC. Therapeutic outcomes were significantly worse (P < 0.001) in WDNET-G3. Patients with KRAS mutations and Rb loss showed a significantly high RR to platinum-based chemotherapy (77\% and 80\%, respectively) than the normal group (23\% and 24\%, respectively). Conclusion: WDNET-G3 and PDNEC show distinct clinicopathological characteristics. Especially, WDNET-G3 does not respond to platinum-based chemotherapy. Rb immunolabeling and KRAS mutations were useful in differentiating between WDNET-G3 and PDNECs. Keywords: net g3, nec, kras, rb
REMINET: A European, Multicenter, Phase II/III Randomized Double-Blind, Placebo-Controlled Study Evaluating Lanreotide As Maintenance Therapy after First-Line Treatment in Patients with Non-Resectable Duodeno-Pancreatic Neuroendocrine Tumors

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Introduction: Patients (pts) with metastatic or locally advanced, non-resectable, grade 1 or 2 Well-differentiated duodeno-pancreatic (WDDP) NETs are treated following European guidelines. Pts with aggressive disease, i.e. progressive and/or symptomatic metastases and/or with significant hepatic invasion (> 30-50%), and/or bone metastases, anti-tumour therapy should receive systemic combination of chemotherapy once disease control is obtained. Aim(s): The aim is to stop chemotherapy until progression. REMINET is an academic randomized, double-blind, placebo-controlled, phase II/III study designed to evaluate whether lanreotide (LAN) as maintenance treatment after L1 therapy.

Materials and methods: Main eligibility criteria: Adults pts with a metastatic (synchronous or metachronous) or locally advanced, non-resectable, grade 1 or 2 WDDP NETs and documented control disease after L1 therapy at least 4 weeks prior to randomization.

Results: 222 patients will be randomly assigned in a 1:1 ratio to receive 120 mg LAN or placebo, every 28 days, until disease progression or unacceptable toxicity. The aim of the phase II part is to demonstrate a 6-months PFS > 45% in LAN arm. Secondary endpoints are PFS according to central review, overall survival, safety and quality of life. A bio-bank of frozen blood will be constituted.

Conclusion: The study is currently open in France, Germany, Belgium, United Kingdom and Ireland. A total of 25 patients are randomized (NCT02288377). Keywords: duodeno-pancreatic neuroendocrine tumours, clinical trial, maintenance
A Study of S1/Temozolomide (STEM) Regimen in Patients with Metastatic Neuroendocrine Tumors

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Introduction: Both single agent Capecitabine alone or Capecitabine in combination with Temozolomide have activity against neuroendocrine tumors (NETs), however, the role of S-1 in NETs is still unknown. Aim(s): We performed a study to evaluate the safety and efficacy of S-1 plus temozolomide (STEM) regimen in patients with locally advanced or metastatic NETs. Materials and methods: A retrospective review was conducted of 14 patients with locally advanced or metastatic NETs who treated with STEM regimen. 12 (85.71\%) patients had failed to one or more line treatment of somatostatin analogues, Sunitinib, Everolimus, Anlotinib or other chemotherapy regimen. Patients received S-1 at 40mg/m2 orally twice daily on days 1–14 and temozolomide 200 mg orally once daily on days 10–14 of a 21-day cycle. Patients were followed for evidence of object response, toxicity, and progression-free survival (PFS). Results: 6 patients (42.85\%) achieved a partial response (PR), and 6 patients (42.85\%) had stable disease (SD). Clinical benefit (PR and SD) was 85.70\%. Median progression-free survival is not achieved. Only 1 patients (7.14\%) experienced grade 3 adverse events. For different origin NETs, a total of 3 (37.50\%) and 4 (50.00\%) pancreatic NETs experienced PR and SD, respectively. A total of 3(50.00\%) and 2 (33.33\%) nonpancreatic NETs experienced PR and SD, respectively. Conclusion: STEM regimen is exceptionally highly active, well tolerated in patients with locally advanced or metastatic NETs. Keywords: neuroendocrine tumors, chemotherapy, s1, temozolomide

Neuroendocrinology 2017;105(suppl 1): 1-338
Clinical Outcomes of Systemic Chemotherapy in Patients with High Grade Neuroendocrine Carcinoma of Biliary Tract

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Introduction: Neuroendocrine tumor of biliary tract is very rare and clinical outcomes of advanced neuroendocrine tumors of biliary tract has not been well demonstrated. Aim(s): We retrospectively analyze the treatment outcomes of systemic chemotherapy in patients with neuroendocrine tumor of biliary tract. Materials and methods: Between January 2012 and October 2014, 8 patients with neuroendocrine tumor of biliary tract who received systemic chemotherapy were identified and included. Baseline clinicopathologic characteristics and clinical outcomes were retrospectively reviewed. Results: Gallbladder was the most common primary site (n=6, 75%) followed by ampulla of vater (n=1) and extrahepatic bile duct (n=1). Tumor grade of all patients were grade 3 according to the WHO criteria. Six patients (75%) had metastatic/recurrent disease and 2 patients were treated for locally advanced disease. Etoposide plus cisplatin chemotherapy was used in all but one patient who received 5-flourouracil/leucovorin. In 6 patients that response assessment was available, partial response was achieved in 3 patients (50%). Progressive disease was the best response in 2 patients (33%). At the time of analysis, 5 patients (63%) were dead. Median survival of overall patients was 11.8 months (95% confidence interval 0.0-32.7). Conclusion: This case series showed that high grade neuroendocrine carcinoma of biliary tract showed comparable clinical outcomes with adenocarcinoma of bile duct and gallbladder. Keywords: biliary tract, high grade, neuroendocrine carcinoma
Introduction: To date no systematic prospective trials have been carried out to evaluate safety and efficacy of unconventional doses of somatostatin analogs (SSAs) in neuroendocrine tumors (NETs). However, dose escalation of SSAs is a common strategy. **Aim(s):** High doses (HD) lanreotide (LAN) therapy in PD NETs **Materials and methods:** A multicenter, prospective, open label, single arm phase II study with LAN ATG (180 mg/28 days for 12 months) has been completed in 35 patients (pts) with PD NETs in standard SSAs. Primary endpoint was safety, secondary efficacy. **Results:** Due to 3 screening failure, the population for safety and intention-to-treat was 32 pts (F 10, mean age 63±11 ys), 16% thoracic and 84% gastroenteropancreatic NET, 49% were G2, and 94% were enrolled for radiological PD. According to RECIST there was an overall response rate, defined as complete response (CR) + partial response (PR) + stable disease (SD), in 44% of pts (3% PR + SD 41%). A radiological PD determined a 34% drop out, clinical PD 10%, while discontinuation occurred in 12% (for various reasons). Median time-to-progression was 11 months. Nine serious adverse events (SAE) in 8 pts have been recorded, including 2 treatment-related (cholelithiasis and cholecystitis), with a SAE frequency rate of 25%. Binomial test (with null hypothesis value at 65%) confirmed that the study met the primary endpoint, showing that treatment with HD LAN is safe (p<0.0001) **Conclusion:** These results support a further development for the use of unconventional doses of SSAs in pts with PD NETs **Keywords:** ssa, high dose
STREET - Somatostatin Treatment Experience Trial

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Introduction: Somatostatin analogs (SSA) delay progress and decrease symptoms in patients with gastroenteropancreatic neuroendocrine tumours (GEP-NETs). It is not known whether patients’ experiences of injection treatment differ between different SSAs. Aim(s): To investigate quality of life and treatment experience with SSA in patients with GEP-NETs. Materials and methods: A cross-sectional study was performed in two Swedish NET centres. Patients with GEP-NET, older than 18 years, with SSA-treatment for less than 3 years and with Ki67<10% were eligible and identified from hospital databases. Patients were sent a questionnaire addressing practical aspects of, and patient anxiety during the most recent SSA injection. Results: Out of 156 patients, 119 (76%) returned a valid questionnaire. Their mean (range) age was 64 (25-83) years, 66 patients (55%) were treated with octreotide and 53 (45%) with lanreotide. In all, 12 (18%) of the patients treated with octreotide reported problems of any kind with their most recent injection compared to no (0) patients on lanreotide (p=0.001). A total of 7 (11%) of patients treated with octreotide reported that they felt moderate to high anxiety before the injection compared to 1 patient (2%) treated with lanreotide. Conclusion: Patients treated with lanreotide reported fewer injection problems and experienced less anxiety before receiving the injection compared to patients treated with octreotide. Keywords: somatostatin analogs, octreotide, lanreotide, quality of life, injection
Therapeutic Strategies in Patients with Neuroendocrine Neoplasm: 30 Month Follow-Up of Long Survivors from EPH Mostaganem and EHU Oran Medical Oncology

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Introduction: Neuroendocrine tumors are poorly known and infrequent tumors, most of the time, diagnosed late, often occurring between the age of 40 and 60. They mainly appear in the gastrointestinal system, pancreas, bronchi, lungs, thymus and thyroid. Aim(s): The main goal of our study is to determine therapeutic epidemiological prognostic characteristics of NeT within our Department

Materials and methods: Thirteen (13) cases had been experienced within the periods of 2015 & 2016 in a retrospective study conducted by the EHU Oran and MOSTAGANEM medical Oncology

Results: Average age was 60, with an age range from 16 to 71. Tests concerned six (6) males (46.60%) and seven (7) females (53.39%). The seat was mainly digestive. In three extra digestive cases, eleven (11) patients with this disease showed to be metastatically. Two (2) of them were not (metastatically). One of the two became metastatic. The zone of metastasis was mainly hepatic for the digestive tract TNE, cerebral in one case for TNE and mainly pulmonary. A rare case of Valerian Ampulmona; the very first case in Algeria. Diagnosis of THE had been obtained by immunohistochemistry. in total cases with chromonogranim and synaptophysin revealed to be positive in 80% of cases. Ki67

Conclusion: Managing TNE’s is complex and needs to be performed by multi disciplinary Teams in order to ensure proper care and define different therapeutic lines according to scalability and treatment available

Keywords: neuroendocrine tumors, metastasis, somatostatin analogs
Escalated Dose Somatostatin Analogues for Anti-Proliferative Effect in Gastroenteropancreatic Neuroendocrine Tumours (GEPNETS): A Systematic Review

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Introduction: Somatostatin analogues (SSAs) are the cornerstone of systemic therapy for well-differentiated GEPNETs. Dose escalation of SSAs is often trialled in clinical practice, but small studies have yielded mixed results.

Aim(s): To determine the benefits and harms of escalated dose SSAs in treatment of metastatic GEPNETs.

Materials and methods: Eligible trials of dose-escalated SSA (more than 30mg octreotide or 120mg lanreotide every 28 days) were identified from major databases and conference proceedings. Disease control rate (DCR), objective response rate (ORR), biochemical response, symptomatic improvement and toxicity were abstracted. Trials were synthesized qualitatively.

Results: Nineteen studies (1098 patients) were identified, 12 prospective and 7 retrospective. DCR ranged from 30-100%, but ORR was modest at 0-14%. Rates of biochemical improvement (27-100%) and symptom improvement (23-100%) ranged widely depending on the population studied and definition of response. The most common toxicities were fatigue, diarrhoea, abdominal discomfort and cholelithiasis, with no severe or unexpected toxicities compared to standard dose SSA.

Conclusion: Escalated dose SSA is well-tolerated in patients with GEPNETS. While a significant number of patients experienced disease control, ORR was low, and exact rates of biochemical or symptomatic response were difficult to judge. There is a need for large, prospective studies investigating the role of escalated dose SSA in the treatment of metastatic GEPNET. Keywords: escalated dose, octreotide, lanreotide, ssa
An Exploratory Patient Centric Analysis of the ELECT Trial: A Phase 3 Study of Efficacy and Safety of Lanreotide Autogel/Depot (LAN) Treatment for Patients (pts) with Carcinoid Syndrome (CS)

Introduction: In ELECT, LAN 120mg every 4 weeks significantly reduced octreotide rescue therapy use for symptomatic CS control vs placebo (PBO).

Aim(s): This patient centric analysis explores the treatment effect on patient benefit during this trial. Materials and methods: The analysis used all patient-reported outcomes collected during the double-blind phase of ELECT: daily diarrhea and flushing symptoms, octreotide rescue use and EORTC QLQ-C30 and QLQ-GINET.21 questionnaires at baseline and week 12. We applied principal component (PC) analysis on the baseline data to identify independent variable clusters, identified summary measures that were highly correlated to these PCs, derived minimum clinical important differences (MCID) and performed a responder analysis. Results: The 3 largest PCs captured 42.9% of the variation among the baseline variables. The C30 summary score (C30-SS), diarrhea burden (BD) and flushing burden (BF) were highly correlated with PC1, PC2 and PC3, respectively. LAN pts had a higher response rate for the C30-SS score (RR 2.42; P=0.023), BD (RR 2.42; P=0.002) and BF (RR 1.28; P=0.43) compared to PBO pts. LAN pts had a significantly higher probability of being a responder in at least one of the 3 domains of C30-SS, BD or BF as compared to PBO pts (RR 1.55; P=0.014). Conclusion: This analysis found significantly higher response rates in the BD and QoL domains among LAN carcinoid syndrome pts, which adds to the previously reported significant reduction in rescue medication use. Industry sponsored.

Keywords: ssa, carcinoid, symptoms
Perioperative Carcinoid Crisis during Surgery - Who Benefits from Octreotide?

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Introduction: Carcinoid crisis, as an entity is poorly defined, but can be seen in patients with small bowel NET after open bowel surgery or tumour unrelated procedures as cardiovascular instability (CI) Aim(s): To audit the incidence of CI during procedures and determine the relationship to perioperative octreotide; considering the patient’s underlying disease burden Materials and methods: Patients were identified from the pathology database having had their primary tumour resected in our institution between Jan 2011 and Dec 2015. Our prophylactic octreotide protocol is an IV infusion of 50 µg/hr for 24 hrs prior to surgery Results: 54 patients underwent 65 procedures. 24% (n=13) had carcinoid syndrome prior to surgery. There was no postoperative mortality or direct morbidity related to CI in the 65 procedures. 77% of patients had preoperative octreotide for at least 4 hours. Most procedures (67%) were complicated by CI not related to blood loss (Table 1). 31 detailed anaesthetic charts were available for review.

<table>
<thead>
<tr>
<th>Procedure Type</th>
<th>Octreotide</th>
<th>No Octreotide</th>
<th>Chi χ2</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bowel resection, no liver mets (n=13)</td>
<td>45.5%</td>
<td>50%</td>
<td>p =0.9</td>
<td></td>
</tr>
<tr>
<td>Bowel resection, liver mets (n=9)</td>
<td>50%</td>
<td>100%</td>
<td>p =0.35</td>
<td></td>
</tr>
<tr>
<td>Simultaneous liver/bowel resection (n=9)</td>
<td>87.5%</td>
<td>100%</td>
<td>p=0.6</td>
<td></td>
</tr>
</tbody>
</table>

Conclusion: Octreotide infusion reduces the incidence and severity of CI during surgery - but is not universal. Almost all patients undergoing bowel or liver resection in the presence of liver metastases will have some form of CI during the procedure Keywords: octreotide, carcinoid crisis
**Introduction:** In phase 3 CLARINET study, LAN 120mg every 28 days significantly prolonged progression-free survival (PFS) vs placebo in pts with well-differentiated metastatic enteropancreatic NETs, but limited data exist for somatostatin analogues in advanced lung/thymic NETs. Evidence that TMZ may be active in thoracic NETs is mainly retrospective. **Aim(s):** This prospective study will investigate safety and activity of LAN–TMZ combination in progressive lung/thymic NETs. **Materials and methods:** This Italian open-label phase 2 trial is of LAN 120mg with TMZ 250mg/day (over 5 consecutive days) every 28 days for 52wks (NCT02698410; EudraCT: 2014-005579-10). Accrual goal is 40 adults with unresectable locally advanced or metastatic well/moderately differentiated lung/thymic NETs and baseline RECIST-based progression ≤1yr pre-enrolment; 13 institutions are active to enrol. Results will be available by end 2019. **Results:** Primary endpoint is disease control rate (DCR; complete/partial response or stable disease) at 9mo (RECIST v1.1). Secondary endpoints include PFS, time to and duration of response, time to progression, best overall response, objective response rate, DCR at 12mo, changes in biomarkers (incl. circulating CgA), safety (adverse-event reports, clinical and laboratory tests). MGMT status and methylation will be evaluated. **Conclusion:** ATLANT will provide valuable data on LAN–TMZ in a homogeneous tumour population of lung/thymic NETs. PFS data will inform the primary endpoint of a subsequent trial. Industry sponsored. **Keywords:** temozolomide, lanreotide

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Effect of Treatment with Prolonged-Release Somatostatin Analoguecs on the Concentration of Serum Fibrosis Markers in Patients with Carcinoid Syndrome

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Introduction: A fibrosis is a major local and/or distant complication of neuroendocrine tumours (NETs) of the small intestine secreting serotonin. Tumour cells produce connective tissue growth factor CTGF and transforming growth factor TGFα and TGFβ which locally stimulate fibrosis and cause distant fibrosis. Aim(s): Assessment the level of serum fibrosis markers CTGF and TGFβ in patients with carcinoid syndrome before and after 12 months treatment with prolonged-release somatostatin analogues. Materials and methods: 30 patients with carcinoid syndrome, the serum level of serotonin, CTGF and TGFβ and 24-hour urinary 5-hydroxy indoles acetic acid (5-HIAA) before and after 12 months of treatment with somatostatin analogues were the subject of researches. The control group consisted of 20 healthy individuals. Results: The levels of CTGF, TGFβ, serotonin and 5-HIAA in patients with NETs were substantially decreased after treatment with somatostatin analogues (p<0.05). Significantly higher levels of fibrosis markers were observed in the group of 8 patients with local and distant fibrosis (p<0.001). A positive correlation between the levels of CTGF and serotonin (p<0.001) as well as urine 5-HIAA (p<0.05) was established. A similar correlation was observed between the levels of TGF β and serotonin (p<0.05) as well as 5-HIAA (p<0.01). Conclusion: Somatostatin analogues significantly reduce levels of CTGF and TGFβ, which may prevent the formation of local or distant fibrotic lesions in patients with carcinoid syndrome. Keywords: fibrosis, ctgf, tgfβ, carcinoid syndrome
Patient Satisfaction Regarding Home Injection Service for Somatostatin Analogues: A Survey among Patients with a Neuroendocrine Tumour

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Introduction: Depot somatostatin analogues (SSA) Sandostatin LAR® (SL) and Somatuline Autogel® (SA) injections are facilitated by a professional home injection service. Aim(s): We have evaluated patient satisfactory in relation to this service. Materials and methods: All patients with neuroendocrine tumours using depot SSA and home injection service ≥ 3 months were approached. A survey was designed with satisfaction related theorems with a five-point Likert scale, multiple choice and free text. Results: 51 patients using SL (23) and SA (28) were included. Satisfaction with information SSA (88%), information service (96%), planning and fulfilment of agreements (94%), administration of injection (92%), knowledge (88%) and technical skills (90%) of the nurse. 74% of patients were satisfied with contacts with customer service. SA (17%) and SL users (52%) experienced at some point problems when administering the injection which result in a non-significant extension of the visit time. Nurses’ visit at the patients’ house took <15 min (16%), 15-30 min (76%), and >30 min (8%). The nurses’ visit for administering SA was significantly shorter (p = 0.048) than for SL. There was no significant difference (p = 0.095) between the duration of the preparation of the SL and SA injection. Conclusion: Overall satisfaction concerning information, communication and injection given by the nurse of the home injection service can be stated as high. Results of this study can be of value for other NET Centres of Excellence. Keywords: somatostatin analogues, home injection
Role of SSA in the Management of Multiple Type 1 Gastric Neuroendocrine Neoplasms

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Introduction: Type 1 g-NENs associated with autoimmune chronic atrophic gastritis have high risk of recurrence but rare metastasis. Most type 1 patients are managed by endoscopic approach. The clinical benefit of somatostatin analogues (SSA) for type 1 g-NENs is controversial. Aim(s): To evaluate the efficacy and safety of octreotide LAR in the treatment of multiple type 1 g-NENs. Materials and methods: From January 2012 to December 2015, a total of 74 pts with type 1 g-NENs were referred to our center (China-Japan Friendship Hospital, Beijing), among them five pts with multiple, small lesions were treated with octreotide LAR (20mg im q28d) for 12 months. After 6 and 12 months of SSA therapy, all the pts underwent gastroscopy with multiple biopsies in the antrum, fundus, body mucosa and the polypoid lesions. The serum gastrin and CgA levels were also determined. Results: Gastric lesions of all 5 pts disappeared at gastroscopy after 12 months of SSA therapy. Pathological examinations also showed no endocrine tumors but ECL cell linear hyperplasia or micronodular hyperplasia in all pts after 12 months of treatment with SSA. A significant reduction of gastrin and CgA levels at 6 and at 12 months of therapy was observed compared with the baseline values. The side effects of octreotide LAR were same as reported previously. Conclusion: SSA treatment can lead to tumor regression and reduce recurrence of type 1 g-NENs. This therapeutic approach should be recommended as one of options for pts with multiple type 1 g-NENs. Keywords: ssa, gastric nen, type 1
Optimisation of the Size Variation Threshold for CT Evaluation of Response in Advanced Gastroenteropancreatic Neuroendocrine Tumors Treated with Octreotide LAR

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Introduction: In advanced gastroenteropancreatic neuroendocrine tumors (GEP-NETs), somatostatin analogs treatment rarely achieve a reduction of -30% in the sum of longest diameters (SLD) of target lesions required by Response Evaluation Criteria in Solid Tumors (RECIST) for an ‘objective response’. The implication of Stable Disease (SD) as an additional indicator of therapeutic effect is often uncertain. Aim(s): We sought to determine a threshold as the reliable early indicator which may derive PFS benefit from this therapy. Materials and methods: Thirty-three patients with well differentiated advanced GEP-NETs (WDGEP-NETs) treated with octreotide LAR underwent thoracic, abdominal and pelvic computed tomography at baseline and at first follow-up after therapy were enrolled. Thresholds from -30% to +20% was defined by the best change in the sum of the longest diameters (ΔSLD) of target lesions, Kaplan–Meier and receiver operating characteristic (ROC) analysis were used to determine the optimal size threshold to distinguish ‘responders’ from ‘non-responders’ with respect to significant improvement in PFS. Results: The optimal threshold for determining a response to octreotide LAR was -10% ΔSLD. At this threshold, median PFS was 20.2 months in responders and 7.6 months in non-responders (hazard ratio (HR), 4.17, 95% confidence interval (CI), 1.64-10.63). Conclusion: Ten percent tumor shrinkage is validated as a reliable early predictor of advanced GEP-NETs patients benefiting from octreotide LAR. Keywords: gep-nets, octreotide lar, progression-free survival
(K12) - SELECTED FOR ORAL PRESENTATION
Efficacy of Lanreotide (LAN), Both Alone and in Combination with Targeted Therapies in a Preclinical Model of Pancreatic Neuroendocrine Tumors (pNETs)


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Introduction: CLARINET trial has proven the antiproliferative effects of LAN in patients with non-functioning gastro-entero-pNETs. However, the combination of LAN with targeted therapies is widely used in clinical practice and should be further evaluated. Aim(s): This study evaluated the effects of LAN treatment, both alone and in combination with targeted therapies (sunitinib and everolimus), in a transgenic mouse model of pancreatic NETs (pNETs).

Materials and methods: 12-week old RIP-Tag2 mice were treated with LAN (BIM-23014 at 10 µg/kg/h minipump infusion) in combination with sunitinib (40 mg/Kg/day) or everolimus (10 mg/Kg/day) by oral gavage, in randomized groups of mice. Combination treatments started two weeks after LAN monotherapy.

Results: LAN monotherapy produced a 42% inhibition of tumor growth (p<0.05) and extended survival of RIP-Tag2 animals (median not reached). Angiogenesis is not involved in this effect; however, evaluation of the effects of treatment on proliferation and apoptosis are ongoing and could reveal the therapeutic mechanism. Combination of sunitinib or everolimus with LAN produced similar efficacy as LAN alone in terms of tumor growth inhibition and survival extension but involved an anti-angiogenic component. Ongoing evaluations may reveal additional mechanisms of combined treatment.

Conclusion: LAN is effective as monotherapy in RIP-Tag2 model of pNETs. Combination of LAN with everolimus or sunitinib is also effective, but involves antiangiogenic effects not observed with LAN alone in this model. Keywords: lanreotide, pnet
Introduction: Zollinger-Ellison syndrome (ZES) can cause severe complications. In multiple endocrine neoplasia type 1 (MEN1) related ZES, surgery has a controversial role and proton pump inhibitors (PPI) are usually first-line therapy, although some concerns regarding long-term use. Somatostatin analogs (SSA) both reduce hypergastrinemia and have an antiproliferative role. Aim(s): Aim of this study is to evaluate efficacy and safety of PPI and SSA in MEN1 related ZES. Materials and methods: Eighteen pts with MEN1 related ZES were retrospectively evaluated (12 m, 6 f, mean age 36 yrs) for a median follow-up of 104 months (range 6-203). Gastrinoma was located in pancreas (7), pancreas and duodenum (7), duodenum(4). All pts were treated with PPI only for at least 6 months (median 12, range 6-19), afterwards SSA were added. Results: Baseline gastrin and Chromogranin A (CgA) were elevated in all pts. After PPI alone, gastrin and CgA remained elevated in 14 pts(78%) and decreased in 4(22%). Complete gastro-intestinal symptom relief was achieved in 50% of pts. After adding SSA, gastrin and CgA decreased or normalized in 17 pts(94%), and remained elevated only in 1(6%). Complete symptom relief was achieved in 16 pts (90%). No radiological tumor progression was observed. No side effects were recorded. Conclusion: SSA in MEN1 ZES, are safe and effective both in reducing hypergastrinemia and clinical symptoms, and allow tumor stabilization too. Prospective studies are required to confirm these data. Keywords: somatostatin analogs, men1, zollinger-ellison syndrome
Results from a Phase 2, Open-Label, Multicenter, Randomized Study of the Novel, Octreotide (Oct) Subcutaneous (SC) Depot Formulation in Patients with Functioning Neuroendocrine Tumors (NETs) and Acromegaly Previously Treated with Long-Acting Octreotide

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I IRCCS AOU San Martino-IST and University of Genoa, Genoa, Italy

Introduction: Oct sc depot is a novel, ready to use formulation administered via a thin needle. Aim(s): To characterize the PK profile and to assess the efficacy, safety and tolerability of oct sc depot vs long-acting oct. Materials and methods: Adult pts with functioning NETs or acromegaly treated for ≥2 months with long-acting oct (10/20/30mg every four weeks [q4w]) received the last dose of long-acting oct in period 0 (P0) and were randomized 28 days later to receive oct sc depot 10mg every two weeks (q2w) or 20mg q4w for 3 months (period 1 [P1]). Results: 12 pts were randomized to oct sc depot 10mg q2w (NET, n=1; acromegaly, n=3) or 20mg q4w (NET, n=4; acromegaly, n=4). In NET pts, steady state (SS) PK (for oct sc depot 10mg,20mg vs long-acting oct 20mg,30mg, respectively) – AUC0-28d(day*ng/L): 83.3,135.0 vs 27.8,39.9; Cmax(ng/mL): 5.61,15.7 vs 1.68,2.48. Symptoms of carcinoid syndrome were similar or improved in P1 vs P0, and disappeared in 2 pts in the oct sc depot 20mg group. In acromegaly pts, SS PK (for oct sc depot 10mg,20mg vs long-acting oct 20mg,30mg, respectively) – AUC0-28d(day*ng/L): 83.3,135.0 vs 27.8,39.9; Cmax(ng/mL): 5.61,15.7 vs 1.68,2.48. Symptoms of acromegaly were similar or improved in P1 vs P0, and disappeared in 2 pts in the oct sc depot 20mg group. In acromegaly pts, SS PK (for oct sc depot 10mg,20mg vs long-acting oct 10mg,30mg) – AUC0-28d(day*ng/L): 95.6,78.5 vs 6.23,24.1; Cmax(ng/mL): 10.6,11.3 vs 0.35,1.41. IGF-1 and GH were well controlled in P1 vs P0. Adverse events were reported in 6 and 8 pts during P0 & P1, respectively (all grade 1-2). Conclusion: Oct sc depot provided higher exposure in both pt populations and was well tolerated with a safety profile consistent with long-acting oct. A phase 3 study is planned to assess the long-term efficacy and safety. Keywords: octreotide sc depot, net
Safety and Efficacy of 14-Day Dosing Interval of Lanreotide Autogel/Depot (LAN) for Patients with Pancreatic or Midgut Neuroendocrine Tumours (NETs) Progressing on LAN Every 28 Days: The Prospective, Open-label, International, Phase 2 CLARINET FORTE Study

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Introduction: CLARINET demonstrated the antitumour effect of LAN 120mg/28 days (standard interval) in metastatic gastroenteropancreatic NETs. If disease progresses (PD) on this dose, aggressive treatments (eg targeted therapies) are usually offered. **Aim(s):** CLARINET FORTE will investigate the safety and antitumour efficacy of instead using LAN 120mg/14 days. **Materials and methods:** Adults with well-differentiated, metastatic/locally advanced, unresectable, functioning/non-functioning, G1/G2, pancreatic (pNETs) or midgut NETs, ECOG PS 0–2, are eligible if radiological PD (central review, RECIST v1.0) occurred with first-line LAN 120mg/28 days ≤24 months previously. Patients (pNETs, n=50; midgut NETs, n=50) will receive LAN 120mg/every 14 days up to week 48 (pNETs)/96 (midgut NETs) unless they experience PD, die or toxicity/tolerability is unacceptable. Unless 25 events occur in each cohort, visits will continue every 12 weeks until PD, death or unacceptable toxicity/tolerability. A data safety monitoring board will oversee the study (NCT02651987; EudraCT–2014-005607-24). **Results:** Primary endpoint: progression-free survival (central review, RECIST v1.0). Secondary endpoints include: overall survival, objective radiological response rate, effect on symptoms, quality of life, LAN PK, safety. Analyses will be descriptive (with exploratory p-values). **Conclusion:** CLARINET FORTE will give insight into a reduced (14-day) LAN 120mg dosing interval for midgut/pNETs progressing on LAN 120mg/every 28 days. Industry sponsored. **Keywords:** lanreotide, dosing interval
**Introduction:** TELECAST assessed telotristat ethyl (TE), a tryptophan hydroxylase inhibitor, in patients (pts) with carcinoid syndrome (CS) with ≥1 CS symptom/sign and a mean 2.5 bowel movements (BMs) per day. Pts were somatostatin analog treated (89%), with gastrointestinal (90%; [diarrhea, 70%]) and cardiac disorders (42%), including carcinoid heart disease. At Week (W) 12, TE (250 and 500 mg 3×/day; tid) significantly reduced urinary 5-hydroxyindoleacetic acid (u5-HIAA) and BMs/day vs placebo (pbo) (p≤0.008). After W12, pts crossed over to an open-label extension (OLE) with TE 500 mg tid (W13–48). **Aim(s):** To provide additional OLE data on TE safety and activity. **Materials and methods:** A 7-day blinded titration was included at OLE start. Safety and efficacy were assessed up to W48. **Results:** 76 pts were randomly assigned; 67 entered the OLE (mean 63.3 years, 58.2% male), receiving (from W13-48) a mean 30 additional weeks of TE exposure (median 36 weeks). The OLE was completed by 47 pts, while 20 discontinued (7 due to adverse events). There were no deaths. No new safety signals were observed in the OLE. Change from study start baseline in u5-HIAA at W12 was +98%, –33% and –76% on pbo, TE 250 and TE 500 mg, respectively, and ranged from –46% to –68% at W18, 24, and 48. Improvements in EORTC QLQ-C30 diarrhea scores on TE were 10–21 points at W12 and 17–18 points at W24 and 48. **Conclusion:** TE was generally well tolerated. Reductions in u5-HIAA and improvement in diarrhea scores were maintained with TE over 48 weeks. **Keywords:** serotonin, safety
Safety and Tolerability of Lanreotide Autogel/Depot (LAN) in Patients (pts) with Neuroendocrine Tumours (NETs): Pooled Analysis of Clinical Studies

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Introduction: Two randomized double-blind (DB) trials demonstrated the efficacy of LAN 120mg/4weeks vs placebo in NETs: PFS improved in metastatic non-functioning intestinal/pancreatic NETs (CLARINET); less rescue medication used for carcinoid syndrome (CS) (ELECT). Aim(s): Pooled data from 5 LAN studies and their extensions provided an overview of safety in NETs. Materials and methods: Data were pooled from CLARINET (96-week DB + ≤6-year long-term open-label [LTOL] extension), ELECT (16-week DB + 3-week initial OL + ≥2-year LTOL extensions) and OL studies of CS symptom relief (6 months), self-administered LAN (7–8 months) and tumour-growth control (92 weeks). Diarrhoea and flushing were excluded for ELECT DB + initial OL phases as they were efficacy measures. Results: Of 378 pts, 90% received LAN 120mg (60/90mg, 10%). AE profiles were similar across studies. 87% of pts had an AE (excl. diarrhoea/flushing), 6% withdrew due to AE, 29% reported ≥1 serious AE, 48% had ≥1 treatment-related (TR)AE. 18 (5%) pts had ≥1 serious TRAE (most frequent: 3 each abdominal pain and cholelithiasis); 13 recovered (2 with sequelae). Most frequent AEs were GI (56% of pts reported GI AEs, excl. diarrhoea; 28% reported diarrhoea), none led to study withdrawal. No deaths were considered treatment related. No additional safety signals were apparent in >12- vs ≤6 month data. Conclusion: These safety data support the positive benefit–risk profile of LAN used for CS symptoms or tumour control in metastatic intestinal/pancreatic NETs. Industry sponsored. Keywords: lanreotide, safety
(K18)
Long-Term Efficacy and Safety with Lanreotide Autogel/Depot (LAN) from CLARINET and Open-Label Extension (OLE) Studies

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\textbf{Introduction:} LAN 120mg has been shown to significantly prolong progression-free survival (PFS) in patients (pts) with gastroenteropancreatic neuroendocrine tumors (GEP-NETs). \textbf{Aim(s):} To examine the long-term efficacy and safety of LAN in pts from the CLARINET and OLE studies.  
\textbf{Materials and methods:} Pts with moderately- or well-differentiated, locally advanced or metastatic nonfunctioning GEP-NETs were randomized to LAN 120mg (n=101) or placebo (PB n=103) every 28 days for 96 weeks (wks). Pts from participating OLE centers with centrally assessed (RECIST 1.0) stable disease at 96 wks (n=56 [LAN, n=41; PB, n=15]) or progressive disease (n=32; PB only) during core study were eligible to receive LAN 120mg every 28 days in the OLE. PFS and overall survival (OS) were analyzed using Kaplan-Meier methods. \textbf{Results:} The median (95% CI) PFS was 154.14 wks (123.57, 237.43) or \textasciitilde39 months for pts initially treated with LAN in the core study who continued with LAN in OLE (n=101) vs 72 wks (48.43, 84.57) or \textasciitilde18 months for pts initially treated with PB (n=103). At the time of final analysis (480 wks or \textasciitilde9.2 years), median OS was not reached in either arm. 64.3\% of LAN/LAN pts and 59.6\% of PB/LAN pts had treatment-related adverse events (TRAEs) during core study and OLE. Diarrhea (18.0\%) and cholelithiasis (14.6\%) were the most frequently reported TRAEs during the OLE. \textbf{Conclusion:} Extended PFS and OS were observed in LAN-treated pts who entered the OLE. Long-term safety of LAN in the OLE was consistent with its known profile. Industry sponsored. \textbf{Keywords:} lanreotide
(K19)
Safety of Lanreotide 120 mg ATG (LAN) in Combination with Metformin (MET) in Patients (pts) with Progressive Advanced Well-Differentiated (WD) Gastro-Intestinal (GI) or Lung Carcinoids. A Pilot, One-Arm, Open-Label, Prospective Study: The MetNET-2 Trial

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Introduction: Anti proliferative effect of LAN ATG 120 mg has been investigated in 204 GI-NET pts in Clarinet study with a 53% reduction in risk of death/progression vs placebo. An increasing number of trials have associated MET with better outcome in cancer pts due to a reduction of insulin/IGF1 levels and modulation of AMPK and TSC1-2/mTOR. The retrospective PRIME-net study conducted on 445 Italian pts, suggest that addition of MET to everolimus and/or SSA provides clinical benefit in diabetic pancreatic NETs. Aim(s): MetNET-2 prospective study evaluates the safety of the combination LAN ATG 120 mg and MET in advanced, progressive GI/ lung NET Materials and methods: 20 G1-G2, WDNET pts, will receive LAN ATG 120mg/28 days and MET 2550mg/day, until progression or unacceptable toxicity. Primary objective is incidence of adverse events (AEs) and severe AEs (SAEs). 1-stage Hern design will be used. The H0 hypothesis (treatment related SAE = 25%) will be tested against a one-sided alternative. H0 hypothesis will be rejected if ≤ 2 pts will experience SAE with a type I error rate of 10% and power of 85%. Expression of 111 genes potentially involved in MET pathway will be assessed by Target NGS approach. Results: Recruitment started in April 2016 and will last 20 months. Study results will be available in 2018. Conclusion: The study will investigate the safety of MET/LAN ATG 120 mg combination; possible synergistic effect of the combination and correlation between mutations and response to therapy will be also assessed. Keywords: lanreotide, metformin
Introduction: Treatment options for advanced lung NETs are limited. The phase 3 CLARINET study demonstrated antitumour efficacy of somatostatin analogue (SSA) LAN 120mg vs PBO for metastatic gastroenteropancreatic grade 1/2 (Ki-67<10%) NETs, but prospective data on SSAs in advanced lung NETs are lacking. Aim(s): This study evaluates safety and antitumour efficacy of LAN 120mg in pts with advanced lung NETs. Materials and methods: SPINET is a large double-blind, PBO-controlled phase 3 study (NCT02683941; EudraCT: 2015-004992-62). Main inclusion criteria are adults with well-differentiated typical/atypical, metastatic and/or unresectable lung NETs, positive SSTR imaging, ≤1 chemotherapy course, ECOG PS0–1. 216 pts from 80 sites across the USA, Canada and Europe will be randomized 2:1 to either LAN 120mg/28 days or PBO, both with best supportive care, until PD/death or unacceptable toxicity. Pts experiencing PD on PBO may opt to receive LAN 120mg in an open-label extension. All pts experiencing PD will be followed to document survival, QoL and subsequent treatment. Recruitment began in July 2016. Results: Primary endpoint is progression-free survival (PFS, time from randomization to PD/death; central review, RECIST v1.1). Main secondary endpoints include PFS according to local review, objective response rate, overall survival, change in CgA, LAN pharmacokinetics, QoL and safety. Conclusion: SPINET is the first prospective randomized trial designed to assess LAN 120mg in typical/atypical carcinoid lung NETs. Keywords: lung nets, lanreotide
Somatostatin Receptor Expression in Adrenocortical Carcinoma

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Introduction: Adrenocortical carcinoma (ACC) is an uncommon neoplasm with an estimated annual incidence of 0.5-2 cases per million population. Surgery of the adrenal tumor is the major treatment. When complete tumor removal is not possible, or in case of recurrence, medical treatment with O,p'DDD(mitotane) is recommended. The treatment of ACC is currently based on the mitotane partial responses have been described in 19-34% of cases, and there are single reports of complete responses. The discovery of somatostatin (SST) and the identification of stable SST analogs with a longer half-life have raised new hopes for the treatment of endocrine tumors. Aim(s): The explore somatostatin receptor protein expression in ACC. Materials and methods: Tumoral adrenal tissues were obtained surgically from 10 patients with ACC (2 men, 8 women; age 44±9). Malignancy was diagnosed according to the histopathological criteria proposed by Weiss. Immunohistochemistry (IHC) was performed with Anti-somatostatin receptor 2 and 5 antibodies. The expression of SSTR 2 and 5 was considered positive if the membrane staining had been presented. Results: Diffuse or focal expression of SSTR 2 or/and 5 was identified in 7 of 10 cases ACC (70%). The expression of SSTR 2 was noted in 3 cases (30%), of SSTR5 in 6 cases (60%). Co-expression was observed in 2 cases (20%). Conclusion: Somatostatin receptor 2 and 5 subtypes are expressed in ACC. This may offer new diagnostic and additional therapeutic possibilities. Keywords: adrenocortical carcinoma, somatostatin receptor, immunohistochemistry
Metabolic Adaptation to Anti-Angiogenic Therapy

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Introduction: Although anti-angiogenic inhibition (AI) therapy has demonstrable efficacy in mouse models of cancer and in certain types of human cancer, responses are typically transitory, followed by resumption of malignant progression that limits survival benefit. Unconventional modes of evasive/adaptive resistance underlay the eventual failures of anti-angiogenic therapy. Functionally established resistance mechanisms include revascularization mediated by alternative pro-angiogenic signals, protection by peri-vascular macrophages and monocytes to induce an immunosuppressive microenvironment, and normal vessel cooption via heightened local invasion and distant metastasis. All three mechanisms have been documented in the prototypical RIP-Tag2 mouse model of multistep tumorigenesis, in which the angiogenic switch is a discrete step in the pathway to invasive pancreatic neuroendocrine cancer. Aim(s): Study evasion from AI. Materials and methods: Preclinical studies Results: New results to be presented identify a fourth mode of adaptive resistance to potent anti-angiogenic therapy in this model: metabolic adaptation, whereby cancer cells adopt distinctive metabolic states which are alternatively fueled by glucose or lactate, in a form of metabolic symbiosis. Conclusion: 1. AI causes acute hypoxia and metabolic compartmentalization 2. Hypoxic cancer cells metabolize glucose and secrete lactate 3. Normoxic vessel-proximal cancer cells import and metabolize lactate, involving mTOR signaling 4. Co-inhibiting mTOR disrupts the metabolic symbiosis Keywords: ai/mtor
Impact of Concomitant Medication on Efficacy of Telotristat Ethyl – A Post Hoc Subgroup Analysis of the Phase 3 TELESTAR Study in Carcinoid Syndrome

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Introduction: The tryptophan hydroxylase inhibitor telotristat ethyl (TE) significantly reduced bowel movement (BM) frequency versus placebo (pbo) in patients (pts) with carcinoid syndrome (CS) in the TELESTAR study. Aim(s): We aimed to explore TE efficacy in subgroups defined by concomitant therapy. Materials and methods: 135 pts with CS and ≥4 BMs/day despite somatostatin analog (SSA) therapy were randomly assigned to receive pbo, TE 250 mg, or TE 500 mg 3×/day. Change from Baseline in BM frequency averaged over the 12-week double-blind treatment (DBT) period was analyzed in subgroups defined by use of high or standard stable dose (SSD) of long-acting (LA) SSA and by concomitant use (yes/no [Y/N]) of short-acting (SA) rescue SSAs, antidiarrheals, and narcotics. High LA SSA was defined as octreotide >30 mg/4 weeks, lanreotide >120 mg/4 weeks, or more frequent dosing of either drug. Results: BM frequency reduction with each TE dose was seen in all subgroups regardless of concomitant therapy; treatment differences versus pbo ranged from −0.67 to −1.11 BMs/day. Mean BM frequency reductions with TE 250 and 500 mg, respectively, by subgroup were: High-dose LA SSA Y/N: −1.34, −1.35 / −1.51, −1.55; antidiarrheal Y/N: −1.51, −1.19 / −1.38, −1.71, SA rescue Y/N: −1.43, −1.29 / −1.44, −1.47, narcotics Y/N: −1.33, −1.68 / −1.48, −1.34. Conclusion: TE produced favorable and consistent effects on BM frequency across LA SSA doses and regardless of concomitant SA rescue SSA, antidiarrheal, or narcotic use in pts with CS. Keywords: serotonin, diarrhea
Sunitinib as First Line Therapy in Patients with Advanced Pancreatic Neuroendocrine Tumors: Experience of a Single Algerian Center

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Introduction: Sunitinib is indicated in the treatment of patients with advanced progressive pancreatic neuroendocrine tumors (pNETs). Its experience as first line therapy is limited. Aim(s): To evaluate efficacy and safety of sunitinib in a cohort of patients with advanced pNETs

Materials and methods: A retrospective review of patients with advanced pNETs receiving sunitinib 37.5 mg daily as first-line therapy between 2011 and 2016

Results: 8 patients (M/F=5/3, median age 45 years), ECOG PS 0-2, all patients had well differentiated morphology, 6 patients had GII pNETs (75%) median ki67 was 10% (range 2-20%), 1 patient had locally advanced tumor and 7 patients had metastatic diseases with 71.4% of liver metastasis (5/7). Median number of received cycles was 11 (31-4). There were 4 objective responses (2 complete responses, 2 partial responses), 2 stabilizations and 2 disease progression. Commonly reported adverse events (GI-GII) were Diarrhea 50%, Neutropenia 25%, Abdominal pain 50% and Palmar–plantar erythrodysesthesia 50%. 2 patients presented severe adverse events: diarrhea GIII, Palmar–plantar erythrodysesthesia GIII and mucite GIII, one of them refused to continue the treatment. After 5 years follow-up, 1 patient died, 2 patients received a second-line treatment, 2 patients had surgery and 3 patients are still receiving sunitinib.

Conclusion: this retrospective analysis suggest that sunitinib as first line therapy is active in advanced pNETs, and reported adverse events were consistent with known safety profile of sunitinib.

Keywords: pNETs, sunitinib, first line
Towards Personalizing PRRT with [177Lu]-Dotatate to Minimise Renal Toxicity in Neuroendocrine Tumour Patients

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Introduction: The kidney is a dose-limiting organ in [177Lu]-Dotatate PRRT (Lutate) and thus renal function is an important prescribing consideration for NET patients. The effect of baseline renal function on kidney absorbed dose is unclear. Aim(s): To investigate the relationship between glomerular filtration rate (GFR) with the fast component of radiopharmaceutical whole body clearance and kidney absorbed dose. Materials and methods: A retrospective study of 19 metastatic NET patients who received 4 cycles of Lutate at our institution. GFR was obtained at baseline (n=19) and post cycle 2 (n=8). Whole body retention of Lutate was measured with the gamma camera at each cycle and radiation absorbed dose to the kidneys was evaluated from quantitative SPECT images. Whole body clearance was obtained from bi-exponential fit to planar whole body images of retained Lutate. Results: Significant correlations were found between GFR and (1) the fast component of clearance (mean 2.14 hrs, r=-0.66, p<0.001) and (2) kidney dose (r=-0.44, p=0.02). For each 10 unit decrease in GFR (mL/min-1), the fast component of clearance increased by c.10 mins and the kidney dose (mean 3.0 Gy/cycle) increased by c.0.24 Gy/cycle. Conclusion: These results indicate that kidney radiation dose can vary by a factor of 2 or greater between subjects with GFR 50-100 + mL/min/1.73m2. This suggests that renal function is an important consideration in personalized radionuclide therapy. Keywords: peptide receptor radionuclide therapy, lutate, renal function, kidney absorbed dose
Comparative Retrospective Analysis of pNETs Treatment with Everolimus (E) and Sunitinib (S)

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Introduction: Two targeted compounds are validated for treatment of pNETs – E and S. Aim(s): We performed retrospective analysis of pts with pNETs treated with E or S. Previously these pts have not been treated with either of these drugs. Materials and methods: 20 pts with progressive pNETs (G1,G2) were treated with E and 16 pts with S 37.5 mg or 50mg dose regimen. All pts were on treatment with long acting octreotide. The mean age was 47 years in E group and 53 in S group. Most pts had liver metastases – 17/20 (85%) in E group and 15/16 (93%) in S group, regional l/nodes – in 6/20 (30%) and 6/16 (38%) and not regional l/nodes in – 4/20 (20%) and 4/16 (25%) pts respectively. Only 4 pts in each group were heavily pretreated with 3 or more lines of chemotherapy. G1 tumor was in 3 pts (E group) and no one in S group. Cytoreductive surgery was performed in 8 (40%) pts (E) and 9 (56%) pts (S). Results: The median PFS was 6.6 months (95% CI: 2.2-11) in E group and 15.9 mths (95% CI: 4.7-27,1) in S group, p = 0.5. 6 pts in E group were treated with S thereafter and median PFS reached only 3.1 mths [95%CI: 0-6,3]. 3 pts in S group were treated with E thereafter and median PFS was 3.4 mths. The main toxicity events were stomatitis, weakness in E group and arterial hypertension in S group. Dose reduction needed more often in E group. Conclusion: In our own experience S seems more effective then E. To establish real difference in efficacy of E and S comparative randomized trial is needed. Keywords: pnets, sunitinib, everolimus
Determination of an Optimal Response Cut-Off to Predict Progression-Free Survival (PFS) in Patients (pts) with Well-Differentiated Advanced Pancreatic Neuroendocrine Tumours (pNETs) Treated with Sunitinib (S): An Alternative to the Current RECIST-Response

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Introduction: Sunitinib prolongs PFS in pNET; RECIST defined-partial responses (PR; \(\geq 30\%\) decrease) are low. \textbf{Aim(s):} We aimed to determine 1) optimal (maximum sensitivity (Se) and specificity (Sp)) RECIST (1.0) response cut-off value to predict progression-free pts at 11 months (m); 2) most informative time-point (highest AUC by ROC analysis and logistic regression) for prediction of benefit (PFS) from S. \textbf{Materials and methods:} Individual data of pNET pts from the phase II and phase III S trials were analysed (post-hoc). \textbf{Results:} Data for 237 pts (85 placebo (P); 152 S [n=66 “50mg 4-weeks on/2-weeks off”; n=86 “37.5mg daily (CDD)”;] and 788 scans were analysed. Median PFS for S and P were 9.3m (95\%CI 7.6-12.2) and 5.4m (95\%CI 3.5-6.01), respectively (HR 0.43 (95\%CI 0.29-0.62); \(p<0.001\)). On S: PR was seen in 19 pts (13\%); median maximum change in sum of marker lesions’ largest diameters (SLD) was -12.8\%. Month 7 was the most informative time-point [AUC 0.78 (95\%CI 0.66-0.9); Odds Ratio 1.05 (95\%CI 1.01-1.08), \(p=0.002\)]. At month 7, reduction of 10\% achieved the highest Se (50\%) and Sp (82\%), amongst cut-offs tested. A 10\% reduction in SLD was associated with improved PFS in the S pts (HR 0.55 (95\%CI 0.3-0.9); \(p=0.04\)); mostly in pts on S CDD (HR 0.33 (95\%CI 0.2-0.7); \(p=0.005\)). A 10\% reduction in marker lesions (p=0.034) and S treatment (p=0.012) independently impacted on PFS (multivariable analysis). \textbf{Conclusion:} Reduction of 10\% is an informative cut-off able to identify pts with significant benefit in PFS from S treatment. \textbf{Keywords:} sunitinib, recist, cut-off
Integrated Safety Analysis of Telotristat Ethyl in Patients with Carcinoid Heart Disease

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Introduction: Release of serotonin by neuroendocrine tumors is associated with carcinoid heart disease (CaHD), which may pose challenges for carcinoid syndrome (CS) treatment. Aim(s): We aimed to examine the safety of telotristat ethyl (TE), a novel tryptophan hydroxylase inhibitor, in a subgroup of CS patients (pts) with a medical history of CaHD. Materials and methods: Adverse event (AE) data were pooled from 2 Phase 3 studies in CS in which 211 pts were randomly assigned 1:1:1 to placebo (pbo), TE 250 mg, or TE 500 mg 3×/day (tid) for 12 weeks and offered open-label 500 mg tid TE in a 36-week extension. Results: The CaHD subgroup consisted of 53 pts: 17, 17, and 19 on pbo, TE 250 mg and 500 mg, respectively. Mean age was 62, 57% were male, and mean body mass index was 23.5. Over the first 12 weeks, the proportions of pts with ≥1 AE were similar among treatment arms. On pbo, TE 250 mg, and TE 500 mg, respectively, study drug discontinuations due to AEs occurred in 2, 3, and 4 pts; severe AEs occurred in 4, 0, and 1 pts; and 6, 4, and 2 pts had serious AEs. There was 1 death and 1 cardiovascular AE on pbo (hospitalization with mitral valve incompetence). The long-term safety profile on open-label TE was similar to that in the first 12 weeks. Short- and long-term safety was similar in pts with CaHD and the overall safety population. Conclusion: The safety profile of TE in pts with CS and CaHD was similar to that of TE in the overall population. Keywords: serotonin, 5-hiaa
Introduction: Medullary thyroid cancer (MTC) comprises 4% of thyroid tumors. 7-23% of patients (pts) have metastases at diagnosis. In some cases metastatic disease follows an indolent course, and in others it progresses rapidly, requiring systemic treatment. Tyrosine-kinase inhibitors (TKI) have demonstrated a median progression-free survival (PFS) of 11 months. Aim(s): To analyze the clinicopathological and molecular features of patients receiving TKI treatment, thus assessing toxicity and efficacy in our practice. Materials and methods: Observational study. Period: January 2008 - May 2016. Statistical analysis: IBM SPSS Statistics 22. Results: 6 pts were analyzed. Median (m) follow-up: 29 months. Age (m): 49 (r 36-73), 4 males. RET mutation: 2 pts. Surgery was performed at diagnosis. All patients presented with more than 2 metastatic sites: lymph nodes (3), liver (3) and bone (2). Locoregional treatment: n=2. CEA (m): 460.5 ng/mL (r 88-1028.3). Calcitonin (m): 3197.50 pg/mL (r 907-20000) at the beginning of the treatment. Median doubling time of markers (n=4) was 22.5 months (r 2.56-47.06). TKIs (n): vandetanib (3), sorafenib (2) and sunitinib (1). Dose reduction was required in 2 pts due to G3/G4 toxicity (hand-foot syndrome and mucositis). Response rate 3 pts (2 EE, 1 PD). TTP: 4.1 months. Conclusion: The short time of follow-up and the variability of the drugs used could justify the shorter TLP of our patients compared to those reported in randomized clinical trials. ITK Treatment is feasible with manageable toxicities. Keywords: tne, tki
Evaluation of the Somatostatin and CXCR4 Chemokine Receptor Expression in Gastroenteropancreatic Neuroendocrine Neoplasms (GEP-NEN) of Different Origin

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Introduction: Somatostatin receptors (SSTR) are known for their overexpression in well-differentiated GEP-NEN, whereas the chemokine receptor CXCR4 is considered to be present mainly in highly proliferative and advanced tumors. Aim(s): Evaluation of potential differences in the SSTR or CXCR4 expression pattern in GEP-NEN in dependence on the place of origin. Materials and methods: Overall, 412 samples from 165 GEP-NEN patients, comprising both primary tumors (PT) and metastases (MTS), originating from different parts of the gastrointestinal tract or from the pancreas were evaluated for the SSTR and CXCR4 expression by means of immunohistochemistry using monoclonal antibodies. Results: The SSTR2A was present in 85% of the PT with a high intensity of expression, followed by the SSTR5 (23%), the CXCR4 (21%), the SSTR3 (10%), the SSTR1 (9%) and the SSTR4 (4%). PT displayed higher SSTR2A and chromogranin A (CgA) expression levels than MTS. Both with PT and with MTS lower SSTR2A and CgA expression levels were seen in tumors originating from the colon or from the appendix as compared to those from other origins. There was a positive correlation between the SSTR2A and the CgA as well as between the CXCR4 and the Ki-67 expression levels. SSTR2A negativity of both PT and MTS was associated with poor patient outcome. Conclusion: The SSTR2A was the most prominent receptor expressed in the GEP-NEN samples investigated. However, expression levels varied considerably in dependence on the location of the primary tumor. Keywords: somatostatin receptor, cxcr4
Sunitinib (Su) in Progressive Pancreatic Neuroendocrine Tumor (PNET) Administered in Different Treatment Lines


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Introduction: Su has shown PFS improvement in patients (pt) with PNET in phase III trial Aim(s): We evaluate metastatic PNET treated with Su after failure of previous treatment (tr) including Everolimus (Ev), to assess efficacy and safety also in late lines of tr, and to evaluate the sequence Su after Ev Materials and methods: From February 2011 to November 2016, 21 PNET pt with progressive disease were treated with Su 37.5 mg orally daily in 5 Italian centers. Grading was G1, G2 and unknown in 4, 15 and 2 pt. Previous tr included SSA, Ev, chemotherapy, PRRT; 1 pt received Su in I line, 4 pt in II line, 6 pt in III line, 6 pt in IV line, 3 pt in V line, 1 pt in VI line. Ev was previously administered in 15 pt. Pt were followed for evidence of toxicity, response using RECIST criteria, and survival Results: On 1 December 2016, in 8 (38%) pt Su administration was ongoing. PR and SD were best response in 5 (24%) and 10 (48%) pt respectively, PD was obtained in 6 (28%) pt. Su showed PR, SD and PD in 2.2 and 1 pt when used in II line or before; in 1.3 and 2 pt when used in III line; in 2.3 and 1 pt when used in IV line; in 1.2 and 1 pt when used over IV line. Median PFS was 7 months (range 1-20+). Stratifying pt according to previous administration of Ev and with PFS <12 months and >12 months, mPFS during Su tr was 6.83 (1-7+) months and 19.8 (1-20+) months, respectively. Higher incidence of G2-G3 toxicities were observed in pt who experience >G2 toxicities to previous Ev Conclusion: Su showed activity in PNET indipendently of previous tr Keywords: sunitinib
Multimodal Treatment of a Metastatic Pancreatic NeuroEndocrine Tumor in Von Hippel Lindau Disease

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Introduction: Von Hippel-Lindau disease (VHL) is an inherited neoplastic syndrome: pancreatic lesions in 35-77\% of cases, usually serous cystic adenoma (SCA), but 5-17\% are non-functioning (NF) NeuroEndocrine tumors (NETs). Aim(s): To report a case of a pancreatic NET in VHL, treated with surgery and targeted therapy Materials and methods: In 2005 a 31-year-old woman with VHL diagnosis presented to our Clinic with sepsis/cholangitis. MRI: 4.0 cm solid-cystic mass of the pancreatic head, multiple pancreatic cysts (up to 3.0 cm). 111\textsuperscript{In}-Octreoscan and 18F-FDG PET/CT both positive for the pancreatic mass. Normal serum tumor markers and GI hormones. Surgery: pylorus-preserving pancreaticoduodenectomy. Results: Histology: well-differentiated (WD) NF-NEC (pT2 N0 M0; Ki67 23.5\%), plus a diffuse SCA. Immunostaining: glucagon (90\%), vasoactive intestinal peptide (90\%). Twenty months later, MRI and Octreoscan showed a single new lesion in the right hepatic lobe. Surgery: excision of 15 metastases of WD-NET in the right hepatic lobe (Ki67 13.5\%). Three months later, CT showed bilobar liver metastases. She started Sunitinib, with stable liver disease, but 2.5 years after second surgery she developed pelvis bone metastases. She was switched to Everolimus, until death for disease progression 5 years after first pancreatic surgery. Conclusion: In VHL pancreatic NETs, consider surgery (if there is a high risk of malignant behavior), and multimodal treatment with anti-angiogenetic agents (Sunitinib). Keywords: von hippel-lindau disease, neuroendocrine tumor, sunitinib
Efficacy and Safety of Low Dose Vandetanib in Metastatic Medullary Thyroid Cancer

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Introduction: Medullary thyroid cancer (MTC) is an aggressive thyroid malignancy. Vandetanib is a tyrosine kinase inhibitor approved for locally advanced or metastatic MTC, administered orally 300 mg/daily. Diarrhea, hypertension and QT prolongation are common side effects and may require withdrawal or dose reduction. Aim(s): Aim of this study was to evaluate efficacy and safety of low dose vandetanib (200 mg/daily) in progressive metastatic MTC. Materials and methods: Clinical, biochemical and radiological records of 6 patients with metastatic MTC were retrospectively evaluated. All pts were negative for RET mutation and had progressive disease after surgery and experimental therapy with pasireotide. Results: Six consecutive pts (3 m, 3 f, median age 61.7 yrs, range 44-79) were treated with vandetanib 200 mg/daily for a median follow up of 17.2 months (range 10-27). Objective response according to RECIST criteria was recorded in 5 pts (4 partial and 1 complete response). One patient experienced progression after 20 months. Serum calcitonin (CT) in pts with objective response, decreased >50% compared with basal CT. Carcino-Embryonic Antigen (CEA) was stable in 2 pts, decreased in 2 pts and increased in 1 pt. The pt with progressive disease had both increased CT and CEA. No adverse effects were recorded. Conclusion: Objective response in 75% of pts, without adverse effects, highlights the efficacy and safety of low dose vandetanib (200 mg/daily) in metastatic progressive MTC. Keywords: medullary thyroid cancer, tyrosine kinase inhibitor
Targeted Therapies (TT) (Sunitinib and Everolimus) for Advanced Gastroenteropancreatic Neuroendocrine Tumors (GEP-NET). A Case Series

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Introduction: Sunitinib (Sun) and Everolimus (Eve) are effective treatments for advanced GEP-NET. Lack of standard treatment sequencing and potential toxicities may preclude its use. Aim(s): to report tolerability and efficacy of TT in oncology practice outside of clinical trial regulations. Materials and methods: Retrospective analysis of GEP-NET patients (pts) treated with either Eve or Sun according to physician’s indication. Results: 43 pts were analyzed. 82% (35) presented pancreatic NETs and 28% (12) non-pancreatic NETs. Sun was indicated in 20 pts; Eve was prescribed for 32 pts. 17% (9) sequentially received both TT and TT was the first line for 27% (14). G3-4 adverse events (AE) with Eve: 15%(5); AE: mucositis 34%(11), anemia 22% (7), rash 16% (5) and diarrhea 16%(5). 12% (4) abandoned Eve due to toxicity and 28% (9) required dose reduction. G3-4 AE with Sun: 15%(3); most common AE: fatigue 40% (8), TSH elevation 30% (6), mucositis 20%(4), diarrhea 20%(4), hand-foot 15% (3) and anemia 15% (3); Sun doses were reduced in 45%(9) and was abandoned in 15%(3). Eve clinical benefit (CB) was 78% (25); with Sun 55%(11) had CB (SD 8; PD 3). TTP with TT was 8 m (Eve 11m; Sun 8.1 m). TTP was shorter in pts who received previous TT (HR 2 [CI95% 1.1-3.6; p0.021]) or if they had TTP from last previous treatment <6 m (HR 2.44, p0.020). Conclusion: In our series Sun and Eve had different toxicity profile, mainly G1-2 AE; with dose reductions TT were well tolerated and obtained CB and TTP similar to reported for EVE. Keywords: tne, therapy target...
A Qualitative Exploration into the Experience of Neuroendocrine Pancreatic Cancer Patients Receiving Molecular Targeted Therapies

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Introduction: Despite extensive efficacy data and limited data examining drug related side effects, the patient experience and quality of life data is limited for this patient group. Aim(s): The focus of this research is to explore the patient experience of receiving Sunitinib and Everolimus. It aims to explore the true lived experience of receiving molecular targeted agents.

Materials and methods: A Qualitative approach was adopted using Phenomenological enquiry, interviews.

Results: Seven patient interviews were analysed reflectively using the Collaizzi Method (Kumar, 2012) and Borton's (1970) analytical Model. 4 emergent themes were identified and a review of current practice. The 4 themes were:

1. "This is not chemotherapy, and I have no just been told I have cancer" 2. "It's just a pill" 3. "This treatment is well tolerated with side effects that are well managed" 4. "Control"

Conclusion: Patients receiving molecular targeted agents require a mechanism of support and information that preserves a sense of control and empowerment. The patient safety and governance issues are paramount, side effects should be closely monitored. Sequencing is an important issue in the support and information needs of patients receiving molecular targeted agents. A formal information session should be available to the patients at diagnosis or their first clinic visit. Patients should receive the additional treatment related session, regardless of the treatment offered. This recommendation could have service provision and staffing issues.

Keywords: sunitinib, everolimus
The Efficacy and Safety of Sunitinib in Patients with Advanced Well Differentiated Pancreatic Neuroendocrine Tumors: Focus on Response Rate

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Introduction: In a pivotal phase 3 study (NCT00428597) SU demonstrated a significant increase in progression-free survival (PFS) vs placebo following early study termination. Aim(s): To support phase 3 data per EMA request.

Materials and methods: In this ongoing, open-label, phase 4 trial (NCT01525550), pts received SU 37.5mg once daily. Eligibility criteria were similar to the phase 3 study. The primary endpoint was investigator-assessed PFS per RECIST 1.0. Secondary endpoints included, PFS per Choi Criteria, overall survival (OS), objective response rate (ORR) and adverse events (AEs).

Results: Overall, 61 treatment-naïve and 45 previously treated pts received SU. At the cutoff date, 82 (77%) patients had discontinued treatment. Median treatment duration was 11.7 months (mo). ORR in treatment-naïve and previously treated pts, respectively, was 23.0% and 20.0% per RECIST and 52.5% and 55.6% per Choi criteria. Using RECIST criteria median investigator assessed PFS (mPFS; 95% CI) was 13.2 mo (10.9–16.7) and mPFS (95% CI) per independent radiologic review was 11.1 mo (7.4–16.6). mPFS (95% CI) per Choi criteria was 18.7 mo (5.6–not estimable) and 16.5 mo (7.4–22.9) in treatment naïve and previously treated pts. Median OS, although not yet mature, was 37.8 mo. Most common AEs were neutropenia (55.7%), diarrhea (50.9%) and leukopenia (43.4%). Conclusion: These results confirm those of the phase 3 study and SU activity in pNETs. ORR was higher based on Choi versus RECIST. AEs were consistent with known SU safety profile. Keywords: pnet, survival, sunitinib
Clinical Features and Outcomes of Advanced PNETs Treated with Sunitinib: Data from CRIPNET-GETNE Study


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Introduction: There are several effective drugs for advanced pancreatic neuroendocrine tumors (PNETs) but the right treatment sequence hasn’t been defined yet. Aim(s): To describe the clinical features and outcomes of the CRIPNET STUDY population, advanced PNETs treated with sunitinib.

Materials and methods: This is a multicentric study supported by Spanish multidisciplinary scientific society GETNE. Overall survival (OS) and progression-free survival (PFS) were compared with Kaplan-Meier and Cox analysis.

Results: 65 patients with advanced PNET treated with sunitinib were recruited between 2008-2016. Clinical features: males 58%, <65years 60%, pancreatic tail primary 74%, all G1-2 and 94% with liver metastases. Previous treatments: 66% primary resected, 14% metastases surgery, 37% chemotherapy (CT), 58% SSA. Sunitinib treatment: 62% concomitant SSA, 52% required dose reduction (14% 2 reductions), 85% dose intensity >25 mg, 5% grade 3 toxicity. mOS: 39.43 months (95%CI, 32.5-46.3). Favorable tendency for non-previous and non-concomitant use of SSA (70 vs 39 & 86 vs 39 months). mPFS: 15.53 months (95%CI, 10.7-20.3). Tendency to better PFS and OS for CT naive patients (18 vs 14 & 46 vs 35 months). No statistical differences in OS nor PFS by sex, ECOG, functioning status, previous SSA or CT, concomitant SSA, dose reduction.

Conclusion: This series from CRIPNET study suggests that sunitinib is a well-tolerated drug showing a favorable tendency to its front-line use and a favorable PFS compared with phase III trial.

Keywords: sunitinib, targeted therapies
Introduction: GSK3 is a serine/threonine-kinase that plays a critical role in cancer. In neuroendocrine tumours (NETs) GSK3 is regularly overactivated.

Aim(s): In this study, we investigated the effects of the GSK3α/β-inhibitor AR-A014418 alone and in combination with lovastatin, everolimus or 5-fluorouracil (5FU) in human pancreatic (BON1, QGP1) and pulmonary (H727) NET cell lines.

Materials and methods: MTS assay, Western blot analysis, FACS, caspase and migration assays were performed to study cell viability, signalling pathways, apoptosis, cell cycle and migration.

Results: AR-A014418 significantly dose- and time-dependently inhibited cell viability in all three cell lines. Synergistic anti-tumour-effects were found in combination with lovastatin in QGP1 and BON1 cells, and with 5FU in QGP1 cells, but not with mTORC1-inhibitor everolimus. GSK3-inhibition induced apoptosis in H727 cells whereas BON1 and QGP1 cells showed another form of cell death. No changes in the cell cycle were seen. AR-A014418 phosphorylated/inhibited GSK3α at low and GSK3β at higher doses (≥20 μM), and showed a compensatory increase of pAKT and pERK at 2h in all three cell lines, potentially explaining the synergism with the ERK- and AKT-inhibitor lovastatin. AR-A014418 inhibited mTORC1/p70S6K and, moreover, reduced cell migration in all three cell lines.

Conclusion: GSK3-inhibition may be a novel therapeutic option in NETs, especially in combination with lovastatin or 5FU, depending on tumour entity.

Keywords: gsk3-inhibition, neuroendocrine tumors, combination treatment
An Open-Label Phase Ib/II Study of Sulfatinib in Patients with Advanced Neuroendocrine Tumors (NCT02267967)

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Introduction: Patients (pts) with advanced neuroendocrine tumors (NETs) who have failed sunitinib or everolimus have limited treatment options. Sulfatinib, a novel kinase inhibitor targeting tumor angiogenesis and immune evasion, has shown encouraging anti-tumor activity in patients with advanced NETs in a phase I study. Aim(s): This is an open-label, single-arm study to further assess the efficacy and safety of sulfatinib in pts with advanced grade 1 or 2 NETs. Materials and methods: Sulfatinib was orally given 300 mg, qd, until disease progression or unacceptable toxicity. Tumor responses were assessed using RECIST v 1.1. Results: A total of 81 pts (41 pancreatic NET, 40 extra-pancreatic NET) were enrolled. The median age was 49 years. The majority of pts had grade 2 diseases (79%) and failed previous systemic treatments (69%). As of November 2016, 12 pts (6 PNET, 6 gastrointestinal NET) had confirmed partial response (PR) and 62 pts had stable disease (SD) with an objective response rate of 14.8% and disease control rate of 91.4%. There were 11 pts who had progressed on previous anti-angiogenesis treatments and all benefited from sulfatinib treatment (3 PRs and 8 SDs). Median PFS has not been reached, but is estimated to be 16.6 months (95% CI: 13.6, 19.4). The most common adverse events were proteinuria, diarrhea, hypertension, TSH elevation and asthenia. Conclusion: Sulfatinib demonstrated promising efficacy and acceptable toxicity in patients with advanced NETs. Two randomized phase III trials are ongoing. Keywords: sulfatinib, net, orr, pfs
An Open-Label Phase II Study to Evaluate the Efficacy and Safety Of PDR001 in Patients with Advanced Well-Differentiated Non-Functional NET of Pancreatic, Gastrointestinal (GI), or Thoracic Origin Who Have Progressed on Prior Treatment

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Introduction: Monoclonal antibody (mAb) inhibitors of immune checkpoints, including anti-PD-1 and anti-PD-L1, have become established treatment (tx) options in various solid tumors. However, there is a paucity of data on checkpoint inhibitors in NET. In a phase I trial of PDR001 (mAb checkpoint inhibitor targeting PD-1) conducted in patients (pts) with multiple solid tumor types, a pt with histologically confirmed metastatic atypical pulmonary carcinoid demonstrated a RECIST-based tumor response and clinical benefit.

Aim(s): This study will evaluate the antitumor activity, safety, and tolerability of single-agent PDR001 in pts with progressive, non-functional NET.

Materials and methods: Pts with non-functional unresectable advanced well-differentiated grade 1/2 NET of GI, pancreatic or thoracic origin who progressed on or after prior available tx will be included. Overall response rate is the primary outcome and duration of response and safety are the key secondary outcomes, respectively.

Results: Ninety pts will be treated by grouping in 3 cohorts of approx. 30 pts each, as per the site of primary NET: GI, pancreatic, or thoracic (including lung and thymic origin). Pts will receive PDR001 (400 mg, once every 4 wks) via 30 min IV infusion for a max tx duration of 24 mo or until disease progression or unacceptable toxicity.

Conclusion: This phase II, open-label, multicenter study will enroll pts in United States, Europe, Canada and Japan (NCT02955069) to investigate the role of immunotherapy in NET after prior tx.

Keywords: pdr001, immunotherapy, net
Biphosphonates in Metastatic Bone Disease of Neuroendocrine Neoplasms

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Introduction: Metastatic bone disease (mBD) in patients with neuroendocrine neoplasms (NENs) is associated with a more aggressive behaviour.

Aim(s): Their response to first line treatment with biphosphonates.

Materials and methods: We studied 554 patients (259 females) with NENs: 94 gastric, 27 duodenal, 201 pancreatic, 70 small intestine, 42 appendiceal, 28 colic, 39 lung, 1 thymic, 32 unknown primary origin (UPO) and 16 elsewhere. Since September 2012 16 patients with NENs and mBD were recruited to receive 4mg of zoledronic acid monthly for 2 consecutive years; they were all followed-up by biochemical parameters and bone scan every 6 months.

Results: 20 (3.6%) patients from the whole cohort had mBD and 1 (2%) of 49 with familiar disease. The prevalence of mBD was: 3 pancreatic, 5.7% small intestine, 3.4% colic, 12.8% lung, 100% thymic, 9.4% UPO NENs. In the biphosphonate study (5 lung, 3 pancreatic, 3 small intestine, 3 UPO, 1 thymic, 1 colic NENS), 5 (31.3%) patients deceased before the 1st semester, and 3 during the study period (1 with progression, 1 with stable mBD, and 1 with improvement followed by stable mBD), 2 (12.5%) patients discontinued treatment because of adverse effects, 3 patients did not complete the study yet, 2 showed progression after stable mBD and 1 stable mBD after an initial improvement.

Conclusion: A 4% of patients with NENs presents mBD that reflects an early aggressive biological behavior being lethal in 50% of treated patients. The positive response after treatment with biphosphonates when tolerated is transient.

Keywords: bone disease
Skeletal-Related Events (SREs) and Use of Antiresorptive Therapy (ART) in Patients with Bone Metastases of Neuroendocrine Neoplasms

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Introduction: Antiresorptive therapy (ART) with bisphosphonates or denosumab is effective in preventing skeletal-related events (SREs) in patients with bone metastases (BM). In neuroendocrine neoplasms (NEN), BM are a negative prognostic factor, however tend to be asymptomatic and SREs are considered rare. The role of ART in preventing SREs in NEN has not been investigated so far. Aim(s): To analyze the impact of ART on development of SREs in NEN patients. Materials and methods: Retrospective analysis of our NEN database for all patients with BM who presented at our center between 08/2013 and 07/2015. Overall survival (OS) from diagnosis of BM as well as time to SRE (TTSRE) was calculated. In patients experiencing an SRE within 1 month after diagnosis (i.e. before efficacy of ART could be assessed), TTSRE was defined as the time to a subsequent SRE Results: In the total of 71 patients identified, median OS was not reached in a median follow-up of 18.8 months. ART was applied to 47.9 % of patients. OS with or without ART did not differ significantly (p=0.7652). 25.4 % of patients experienced SRE, 16.9 % after more than 1 month. Median TTSRE was 63.8 months with ART and not reached without ART (p=0.1751). Conclusion: SREs in NEN patients with BM were not uncommon. Application of ART did not significantly alter median OS or TTSRE. If these results can be confirmed in a larger patient cohort with longer follow-up, the use of ART in NEN should be evaluated prospectively. Keywords: nen, bone metastases, antiresorptive treatment, bisphosphonates, denosumab
Relationship between Symptoms and HRQoL Benefits in Patients (pts) with Carcinoid Syndrome (CS): A Post-Hoc Analysis of Telotristat Ethyl (TE) TELESTAR Trial

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Introduction: TELESTAR previously demonstrated the efficacy and safety of TE in pts with CS experiencing >4 Bowel Movements (BM) per day despite stable-dose somatostatin analog therapy. Significantly higher rates of Durable Response (DR, predefined as Bowel Movement (BM) frequency reduction ≥30% from baseline for ≥50% of the 12 week double blind period) were observed with TE (TE 250mg: 44%, TE 500mg: 42%) vs placebo (20%).

Aim(s): This analysis aims at characterizing the clinical and HRQoL benefit in pts who reached DR. Materials and methods: Changes from baseline to W12 in endpoints were compared between DR and non-durable responders (NDR) irrespectively of treatment arms. Significance was based on 95% CI of difference in means.

Results: Improvement was greater for DRs than NDRs in daily BM (-2.7 vs -0.9), daily flushes (-1.2 vs -0.1), u-5HIAA levels (-52.1 vs -13.4 mg/24h) and abdominal pain (-1.1 vs 0.1). DRs also showed clinically meaningful improvement in QLQ-C30 global health status (8.1 points) and greater increase in summary score (4.9 points) compared to NDRs. Other HRQoL scores suggest greater benefit for DRs versus NDRs in most subscales, with particularly clinical significance on pain. Conclusion: Pts treated with TE presented more DR. DR was associated with meaningful reduction in the overall clinical burden of CS and improvement in HRQoL at W12. Industry sponsored. Keywords: telotristat ethyl, hrqol, carcinoid syndrome

Neuroendocrinology 2017;105(suppl 1): 1-338
Towards Optimal Personalized Diet and Vitamin Supplementation in NET Patients; A Feasibility Study

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Introduction: Patients with a neuroendocrine tumor (NET) often have gastrointestinal complaints due to somatostatin analogue (SSA), tumor mass, secretion of neuroendocrine amines or treatment. This can lead to impaired absorption of critical food components such as vitamins. Serotonin producing NET patients may also have low plasma tryptophan. Aim(s): To explore if personalized dietary advice and supplementation of deficient vitamins is feasible. Materials and methods: Fifteen NET patients using a SSA were counseled by a dietician for a personalized dietary advice and supplementation of deficient vitamins. Feasibility was assessed by calculation of participation/dropout rate and safety. After 4 and 18 weeks, quality of life (QoL), distress, empowerment and nutrition state were assessed. Also, vitamins and tryptophan levels in blood and urine were measured. Results: Participation rate was 75% and dropout rate was 17%. No intervention related adverse events related occurred. A heterogeneous effect was seen on QoL, distress, empowerment and nutrition state. At baseline 8 patients had deficient vitamins. After the intervention, this was resolved in 6 patients. Conclusion: Dietary intervention with supplementation of deficient vitamins is feasible. Our study confirms that NET patients are at risk for vitamin deficiencies. Personalized dietary advice with supplementation of deficient vitamins decreases the number of vitamin deficient NET patients. Industry sponsored (an educational grant). Keywords: diet, vitamin, neuroendocrine tumor, somatostatin

Neuroendocrinology 2017;105(suppl 1): 1-338
(M5)
Web-Based Tailored Information and Support for Patients with a Neuroendocrine Tumor

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Introduction: Patients with a neuroendocrine tumour (NET) frequently experience physical and psychosocial complaints. Novel strategies to provide information to optimize supportive care in these patients are of interest. Aim(s): The aim of this study was to examine whether the use of a web-based system consisting of self-screening of problems and care needs reduces distress and/or improves patients’ perception and satisfaction of received information, quality of life (QoL) and empowerment. Materials and methods: NET patients were stratified between newly diagnosed patients (< 6 months, n=28) and patients with a longer duration of the disease (n=74) and randomised between standard care (n=49) or intervention with additional access to the WBS (n=53) during 12 weeks. Patients completed questionnaires about distress, QoL and empowerment. The intervention group also completed a questionnaire regarding their use of and opinion on the web-based system. Results: From 1 May 2015 until 4 October 2016, 102 patients were included. To date, 72 patients have reached end of study. Dropout rate was 10% (n=8). Median age of included patients was 65 years (range 33-81) and 57% was male. Results of this ongoing trial will be presented. Conclusion: This web-based system can be of added value to standard care for all NET patients when it improves distress, patients’ perception and satisfaction of received information, QoL and empowerment more than only receiving standard care. Industry sponsored (an educational grant). Keywords: neuroendocrine tumor, information, quality
To Treat or Watch? Identifying Drivers of Decisions for Patients with GEP-NET Using Reflective Multi-Criteria Decision Analysis


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Introduction: Somatostatin analogs (SSAs) or watchful-waiting are recommended for unresectable, well- or moderately-differentiated non-functioning GEP-NET. Aim(s): We developed a shared-decision framework and explored drivers of decision. Materials and methods: Using a decision support tool designed from a holistic MCDA-framework (EVIDEM), literature review and patient and physician insights. 5 patients and 6 physicians explored decision drivers in 2 scenarios: SSA (reference case lanreotide) vs observation and lanreotide vs octreotide. Evidence derived from a comprehensive literature review. For each criterion, participants gave a weight, shared experiences and knowledge and assigned a score (+5 to -5 [Much in favor of option 1 vs option 2]). Criteria value contributions (VC) were calculated (NormWeightXScore) and sensitivity analyses performed. Results: For SSA versus watchful-waiting, Type of therapeutic benefit, Disease severity, Effectiveness and Quality of evidence favored SSA (mean VC 0.08±SD0.06, 0.07±0.09, 0.07±0.09, 0.06±0.06 respectively), while Costs favored watchful-waiting. When comparing two SSAs, System capacity (0.02±0.02) and Non-medical costs and constraints (0.02±0.03) favored lanreotide and Cost of intervention octreotide (0.08±0.12). Subcriteria Impact on autonomy and dignity favored lanreotide. Wide SDs reflect variability of perspectives. Conclusion: Reflective MCDA revealed drivers of decision and diversity of perspectives, supporting evidence-informed shared decision making. Keywords: mcda, decision making, gep-net, evidem
The Impact of the Pathologic Differentiation (Well or Poorly) and the Degree of Ki-67 Index in Patients with Metastatic WHO Grade 3 GEP-NETs

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Introduction: There is few data for the treatment-outcome with etoposide plus platinum between well differentiated and poorly differentiated metastatic grade 3 GEP-NEC. Aim(s): Herein, we investigated the impact of pathologic differentiation (well or poorly differentiation) in metastatic grade 3 GEP-NEC patients receiving etoposide and platinum based therapy. Materials and methods: Herein, we investigated the impact of pathologic differentiation (well or poorly differentiation) in metastatic grade 3 GEP-NEC patients receiving etoposide and platinum based therapy. Results: Between well differentiated and poorly differentiated grade 3 GEP-NETs, there was a significant difference for the distribution of Ki67 index. There was no significant difference of treatment efficacy between well and poorly differentiated grade 3 GEP-NECs (the RR; 35.7% vs. 41.2%, p=0.525). Five of 7 patients with Ki67>60% had the tumor response of EP and 7 of 24 with Ki67≤60%, the tumor response. Between patients with Ki67>60% and Ki67≤60%, there was the significant difference of tumor response (the RR; 71.4% vs. 29.2%, P=0.043). There was no a significant difference in PFS according to pathologic differentiation (well differentiated vs. poorly differentiated) and Ki67 index (>60% vs ≤60%). Conclusion: Although the same grade 3 GEP-NECs, there was significant difference for ranges of Ki67 index between well and poorly differentiated NETs. And higher levels (>60%) of Ki67 index might be predictive marker for EP as a standard regimen in grade 3 GEP-NECs. Keywords: ki67 index
Correlation of Plasma (p) and Urine (u) 5-HIAA Levels in Patients (pts) with Carcinoid Syndrome (CS) – Post-Hoc Analyses from the TELESTAR Study

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Introduction: Telotristat ethyl (TE) is an oral tryptophan hydroxylase inhibitor in development for treating CS symptoms. During the double-blind treatment [DBT] period of the phase 3, 12-week, placebo-controlled TELESTAR study, TE was well tolerated and significantly reduced bowel-movement frequency and u5-HIAA levels compared with placebo (PBO) in NET patients with CS treated with a SSA. Aim(s): u5-HIAA is a commonly used serotonin marker in CS. Here, we investigated the potentially convenient alternative p5-HIAA.

Materials and methods: During DBT, 24h u5-HIAA and p5-HIAA levels were measured at baseline and every 6 weeks. Correlations were analysed between u5-HIAA and p5-HIAA at baseline, and 6 and 12 weeks. Results: Baseline mean u5- and p5-HIAA values were 87.6 (±140.8) mg/24h and 331.5 (±574.7) ng/mL, respectively. Mean u5-HIAA changes from baseline averaged across all time points were –40.6 mg/24h (n=45) for TE 250 mg, –54.3 mg/24h (n=45) for TE 500 mg and –5.5mg/24h (n=45) for PBO. Corresponding p5-HIAA levels were –59.1 ng/mL (n=44), –133.9 ng/mL (n=41) and +58.8 ng/mL (n=40), respectively. Spearman correlation coefficients for u5- and p5-HIAA were 0.93 (p<0.001) at baseline, 0.83 (p<0.001) at week 6 and 0.89 (p<0.001) at week 12. Conclusion: In pts with CS in the TELESTAR study, u5- and p5-HIAA levels were significantly correlated independently of treatment. Further analyses are needed to validate the use of p5-HIAA in daily clinical practice for the management of NET pts. Industry sponsored Keywords: carcinoid syndrome, 5-hiaa, telotristat
Metachronous Pancreatic Neuroendocrine Tumors. An Unusual Interesting Case Report

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Introduction: Literature surveillance state that in multiple endocrine neoplasia (MEN) disease, frequently occur, synchronous or metachronous neuroendocrine tumors (NETs) but in non-MEN patients are extremely rare. Aim(s): The main objective is to present an interesting unique case Materials and methods: A male 70-years-old presented with pancreatic mass and liver lesions. Results: A biopsy recorded G2 pancreatic neuroendocrine tumor. The immunohistochemically stain revealed: synaptophysin, chromogranin, PDX-1, ISL 1, CDX-2, PAX-8, Insulin positive expression. The ki-67 index was 10%. The patient started on somatostatin analogue, capecitabine/oxaliplatine and partial response documented. He continued on bevacizumab/flouracil/irinotecan with stabilization of lesions. He was in excellent status with no imaging or clinical deterioration. On the sixth year, some liver lesions increased. A new biopsy confirmed G3 pancreatic neuroendocrine tumor: synaptophysin, chromogranin, PDX-1, ISL 1 negative, CDX-2 checked positive and PAX8 and Insulin were negative. Index ki-67 was 85%. The ATRX in both biopsies were negative, met in liver metastases, predictive of bad prognosis. Both morphologic and immunophenotypic findings were different between the biopsies samples taken on the onset of the disease and at the progression time, supporting the distinct entities. The patient, due to the newly malignancy, started on on platinum based regiment with etoposide Conclusion: It is important to be suspicious of development of different neoplasms origination Keywords: pancreatic
Selective Transarterial Embolization of Gastro-Entero Pancreatic (GEP) Neuroendocrine Tumors (NET) with Advanced Locoregional Disease and/or Liver Metastases

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Introduction: Selective transarterial embolization (TAE) and chemoembolization (TACE), are alternative options to systemic therapies in patients with GEP-NET G1/G2 with advanced locoregional disease and/or unresectable liver metastases. Aim(s): We report clinical-Rx outcomes in 7 patients who received TAE/TACE from Oct 2015 to Oct 2016, to assess the potential benefit of this treatment. Materials and methods: TAE was performed using beads 200 microns in diameter, loaded with 150 mg doxorubicin in TACE. Tumor necrosis was evaluated according to modified RECIST using computed tomography 1 month after treatment. Results: We performed 16 TACE/TAE on 7 patients with G2 NET (Ki-67 5-15%): 6 patients with nonfunctional pancreatic NET (pNET) and one patient with unknown primary site NET and carcinoid syndrome. Patients had previously been treated with surgery (4), somatostatin analogs (4), everolimus (1) or BEZ 235 (1). 4 patients with unresectable bilobar liver metastases, were treated with an average of 3 TACE sessions. A mean of 15 liver metastases were embolized. Their average maximum diameter was 64 mm. The mean percentage of necrosis was 75% (60-85%). 3 patients with pancreatic NET and non resectable locoregional disease were treated with TAE. The maximum diameters were 110, 37 and 38 mm. The mean percentage of necrosis was 75% (70-90%). The most common side effect of TACE/TAE was post-embolization syndrome. Conclusion: TACE/TAE was effective in patients with GEP-NET and advanced locoregional disease or unresectable liver metastases, to reduce the tumor burden. Keywords: tace, tae, gep-net
Introduction: Prediction of PRRT efficacy is critical. We tested a blood-based multigene NET transcript analysis (NETest) to predict efficacy in 2 PRRT-treated NET cohorts. The algorithm comprises >50 genes + clusters of growth factor signaling (GFS) and metabolism (MTB). Aim(s): To predict efficacy of PRRT. Materials and methods: We studied 2 independent 177Lu-PRRT-treated groups: #1 (n= 72), median total activity 18.5GBq (6.5-27.8) and #2 (n= 41), 24.5GBq (11.4-29.7, 24 evaluable pts). At baseline: Ki67, SSR imaging (SRI), CgA (ELISA), and NETest (qRT-PCR - multianalyte algorithmic analyses). Using #1 we mathematically devised a predictive response index (PRI) of NETest (MTB+GFS) & Ki67. We then assessed PRI in #2. RECIST criteria were used. Statistics: multiple regression, Kaplan-Meier survival, Chi2. Results: Cohorts were comparable by grade, staging, and SRI uptake. #2 had more baseline progressive disease (p<0.01), and NETest levels were more elevated (67±6% vs. 51±3%, p=0.03), while CgA was similar (644±133 vs. 684±295ng/ml). At restaging, disease control rates were similar (68% and 83%, p=0.23) and median PFS was not reached in either cohort. PRRT response was not predicted by grading (p=0.15), SRI (p=0.41) or CgA (p=0.12). In #1 PRI accurately (>90%) predicted responders (95%) and non-responders (90%), better than SRI (p<0.0001). In #2 PRI was also predictive (83%) and more accurate than SRI (p<0.01). Conclusion: Pre-therapy NETest accurately predicted (83-94%) PRRT efficacy and outperformed (p<0.01) CgA, Ki67 and SRI. Keywords: prrt, efficacy
Introduction: Radioembolization (RE) is applied worldwide in patients with liver-dominant metastatic neuroendocrine tumours (mNET). Current literature is of poor quality and based on small heterogeneous populations. Aim(s): Aim of this study was to assess efficacy and toxicity of RE with yttrium-90 resin microspheres in mNET in a large international multicenter retrospective study, to address shortcomings in current literature. Materials and methods: Only patients with baseline and follow-up CT/MRI were included. Demographic, clinical, laboratory, and imaging parameters were collected. Efficacy was assessed according to RECIST 1.1 and clinical response. Biochemical toxicity was based on CTCAE v4.03. Results: A total of 244 patients (pNET=85, small bowel=85, large bowel=23, unknown origin=34, other=16) with different grades (G1 39%, G2 35%, G3 10%, unknown 15%) receiving their first RE were included. RE resulted in CR 1%, PR 13%, SD 77%, PD 9% according to RECIST 1.1 after 3 months. New grade 3-4 biochemical toxicities were limited (lymphocytopenia 6.7%, others <2.5%). In symptomatic patients (63%), improvement and resolution of symptoms occurred in 44% and 34%, respectively. Clinical toxicities within 3 months after RE were mainly abdominal pain (31%), fatigue (29%) and nausea (26%). RE specific complications were rare (<4%). Median overall survival was 3.7, 2.7 and 0.7 years (p<0.01) for G1, G2 and G3, respectively. Conclusion: In this largest series to date, safety and efficacy of RE was confirmed. Keywords: neuroendocrine tumors, radioembolization, sirt
Pitfalls in the Response Evaluation after Peptide Receptor Radionuclide Therapy with [177Lu-DOTA0,Tyr3]Octreotate

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Introduction: PPRT with [177Lu-DOTA0,Tyr3]octreotate (177Lu-DOTATATE) is a treatment with good results in patients with metastatic GEPNETs. Aim(s): Identify pitfalls that should be taken into consideration when evaluating the treatment response after PRRT. Materials and methods: 354 Dutch patients with GEPNETs who were treated with 177Lu-DOTATATE between March 2000 and December 2011 were retrospectively selected. Liver function parameters and chromogranin A were measured before each therapy and in follow-up. Anatomical imaging was performed before therapy and in follow-up after 6 weeks, 3 months and 6 months and thereafter every 6 months. Results: An increase of the aminotransferases of ≥20% compared to baseline was observed in 83 of 351 patients (24%). In patients with an objective response (OR) and stable disease (SD) this increase was observed in 71/297 (24%) and in patients with progressive disease (PD) in 12/54 patients (22%). An increase in chromogranin A of ≥20% compared to baseline was observed in 76 patients (29%). This was present in 34% of patients who eventually had PD and 27% of patients who had OR/SD. In 70% of patients this tumor marker returned to baseline levels after therapy. Conclusion: Clinicians should be aware that biochemical changes during follow-up after PRRT is not uncommon and may occur due to radiation induced inflammation or to disease progression. Repeated measurements over time are necessary to differentiate between the two. Keywords: 177Lu-dotatate, prrt, response evaluation, toxicity
Predictors of Outcome in Patients Treated with Peptide Radio-Labelled Receptor Target Therapy (PRRT)

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Introduction: The efficacy of PRRT has been demonstrated in patients with well differentiated NETS. The NETTER-01 study demonstrated disease stabilisation or partial response in approximately 80% of patients. However, more studies are needed to identify predictors of response. Aim(s): To investigate the clinic-pathological characteristics in patients treated with PRRT Materials and methods: We performed a retrospective analysis of patients treated from 2011-2016. Patients with at least 1 year of follow-up data from the last treatment were included. Patients with progression within 1 year of finishing treatment (Group 1) were compared to patients with disease stabilisation/response (Group 2). Progression prior to commencement of treatment was defined as either small volume (<20%) or by RECIST

Results: 307 patients underwent PRRT with Lu-177 or Y90 DOTATATE. 66 patients in Group 1 (48 Lu-177, 18 Y90) were compared to 64 patients in Group 2 (43 Lu-177, 21 Y90). Median survival in Group 1 was 21 months vs 35 months in Group 2 (p<0.002). More patients in Group 1 had greater than 50% liver volume (p<0.0001). Mean CgA was in Group 1 was 1250pmol/L vs 608pmol/L in Group 2 (p<0.03). 18 patients in Group 2 had small volume progression prior to treatment compared to 6 in Group 1 (p<0.003) Conclusion: Radiological progression with 12 months of completion of PRRT is associated with worse survival. Patients with greater liver involvement and highest CgA levels are more likely to progress. Earlier treatment with PRRT should be considered

Keywords: prrt, y90, lu-177
Dosimetric Analyses of Patients with Metastatic Gastrointestinal Neuroendocrine Tumors Treated with PRCRT Using 177 Lu-DOTATATE with Capecitabine as Radiosensitizer

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Introduction: Peptide Receptor Radionuclide Therapy with 177Lu-DOTATATE is gaining acceptance as safe and effective therapy for inoperable neuroendocrine tumors (NET). A radiosensitizing chemotherapeutic drug - capecitabine, the prodrug of 5-Flourouracil, is included in the protocol to further enhance therapeutic efficacy. Aim(s): To assess the biodistribution and present reasonable estimates of normal organ doses to liver, spleen and kidneys using 177 Lu-DOTATATE and Capecitabine. Materials and methods: Fifteen patients (mean age 51.4y) of metastatic gastric-intestinal NETs diagnosed with 68Ga-DOTANOC PET-CT,histopathology and biochemical markers were were prescribed oral tablet capecitabine in dose of 500mg/m2 twice daily for 14 days, commencing 9 days prior to PRRT. 6.66 to 7.4 GBq (180-200 mCi) of 177Lu-DOTATATE was infused to each patient with co-infusion of amino acid solution for renal protection. Each patient underwent whole-body scans at 2, 24 and 96 hours post therapy. The organs included in dosimetry were kidney, liver, spleen and tumor sites. All calculations were done using HERMES software Results: Radiation absorbed doses were calculated as 0.27±0.11 mGy/MBq for kidneys, 0.32±0.19 mGy/MBq for liver and 0.60±0.34 mGy/MBq for spleen. Average effective dose was 0.05±0.01 mGy/MBq Conclusion: The safely administrable maximum cumulative activity of 177Lu-DOTATATE within permissible renal threshold (23Gy) was found to be 73 GBq. However, considerable interpatient differences in absorbed dose of all organs were seen. Keywords: prrt, radiosensitizer
Initial Experience of a Novel Endoscopic Full Thickness Resection Device (FTRD) for the Treatment of Rectal Neuroendocrine Tumours

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Introduction: Standard endoscopic resection of rectal NETs is often associated with histological incomplete excision due to submucosal position within the bowel. Endoscopic full thickness resection may allow early definitive management. Aim(s): To assess the effectiveness of the FTRD in the management of small rectal NETs. Materials and methods: Review of all rectal NET patients presenting to the regional NET multidisciplinary team meeting between January 2015 and August 2016. Full thickness resection performed using an over-the-scope device. Results: 17 patients, 9 male with median age 55 years. Rectal NET was identified at bowel screening(7); endoscopic investigation of rectal bleeding(4) & diarrhoea(3); colorectal cancer surveillance(1) and unrecorded in (2) patients. There were 14 grade1 NETs: 13 T1 tumours underwent endoscopic treatment and 1 T3 tumour had surgery. Of those 13 patients, 10 had initial polypectomy with incomplete excision in 5; 2 went on to FTRD of the scar which confirmed complete excision; 1 patient awaiting FTRD. 3 remaining patients underwent initial FTRD, all with complete excision. No FTRD related complications. Of remaining 3 patients, 1 was grade 2: underwent TAMIS surgical excision and 2 grade 3: 1 surgical resection & 1 systemic treatment for metastatic disease. Conclusion: FTRD is a promising technique offering a simple and safe method to obtain or confirm complete endoscopic excision, thus enabling early definitive management of small low grade rectal NETs. Keywords: endoscopic full thickness resection, rectal net

Neuroendocrinology 2017;105(suppl 1): 1-338
Eleven Years Survival after Combined Treatment of Surgery, Ultrasound-Guided Radiofrequency Ablation of Liver Metastasis, CT Embolization Plus Somatostatin LAR in a Case with Atypical Carcinoid of the Lung

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Introduction: The combination of different therapeutic methods has an important place in the treatment of patients with NET and liver metastasis, ineligible for radical surgery. Aim(s): We report a case with atypical carcinoid of the lung with eleven years survival after combined treatment of surgery, ultrasound-guided radiofrequency ablation of liver metastasis, CT embolization plus octreotide LAR. Materials and methods: The case was a female, 63-years old, with carcinoid syndrome due to an atypical carcinoid of the lung and multiple well differentiated neuroendocrine liver metastasis. The therapy included surgery, ultrasound-guided radiofrequency ablation of liver metastasis, CT embolization plus octreotide LAR. Results: Carcinoid syndrome started at 2005 y. followed by lobectomy of the right lung (2006). The presence of multiple liver metastases was confirmed (2011). Octreotide LAR was introduced (2011), and multiple sessions of ultrasound guided-radiofrequency ablation were carried (2012, 2014, 2015). At 2016 CT angiography and CT embolization of AV malformation in the system of a. heptatica using epirubicin-loaded TANDEM microspheres 100 μm were done. Conclusion: Combined therapy by surgery, multiple sessions of radiofrequency ablation, CT embolization and octreotide LAR lead to significant improvement of severe carcinoid syndrome and prolongation of survival in the patient with atypical carcinoid of the lung and nonresectable neuroendocrine liver metastasis. Keywords: atypical carcinoid of the lung, liver metastasis
A Hybrid Clinical Molecular Nomogram Accurately Predicts Survival in PRRT Treated GEP-NETs

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Introduction: Clinical assessment has limited prognostic ability. Mathematical tools –nomograms- that incorporate multiple parameters are more effective. Novel transcriptomic data has added value in defining NET biology in tissue and blood. A blood multigene expression analysis test is effective as a molecular prognostic marker for PFS. Aim(s): Design a combined clinical and gene expression nomogram (CGEN) to predict OS and PFS in PRRT-treated GEP-NETs. Materials and methods: 177Lu-PRRT-treated GEP-NETs (n=57) were followed: median 15 months (range 1-33). Clinical nomogram data included 10 variables (age, gender, grade, Ki67, stage, symptoms, liver mets, SSA use, surgery, CgA). Hazard ratios were calculated for the clinical nomogram (10) and 51 NET transcripts (Cox-proportional modeling) to design a hybrid nomogram. OS and PFS (RECIST criteria) were analyzed (ROC, Kaplan-Meier survival). Results: The median OS was not reached (8 deaths); mPFS was 19 months. Grade and stage were ineffective predictors. The clinical nomogram, NETest and CGEN scores were significantly higher (p<0.04) in non-survivors. For OS, the AUC for the clinical nomogram and NETest was 0.55-0.60 (p=NS), but for the CGEN it was 0.84±0.05, (p=0.002) (100% survival predicted). The CGEN also accurately predicted PFS (p<0.008); the mPFS was 17 months vs not reached. Conclusion: A hybrid clinical-molecular nomogram using circulating NET transcripts accurately predicts OS and PFS in PRRT-treated GEP-NETs. Keywords: prrt, nomogram, netest, biomarker, os, pfs, prediction
Predictive Value of Baseline Hematology Parameters on Outcome of 177Lu-DOTATOC PRRT

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Introduction: In external beam radiotherapy it has been well established that improved tissue O2 increases therapy efficacy, likely mediated by O2 derived free radicals. Additionally, emerging evidence suggests immuno-stimulatory effects of radiotherapy through activation of lymphocytes. Aim(s): In PRRT the relevance of tissue O2 and immuno-stimulation have not been evaluated to date. Therefore, we compared baseline hematology parameters with PRRT efficacy. Materials and methods: 56 patients with metastasized, progressive and DOTATOC uptake positive NET were treated with 177Lu-DOTATOC. Patients received on average 2.1 (range 1 – 4) cycles of 7.0 GBq every 3 months. Efficacy was analyzed with RECIST 1.1. and classified as complete response, partial response, stable disease or progressive disease and correlated with baseline Hb, erythrocytes, leukocytes, lymphocytes, neutrophils and platelets. Kruskal-Wallis test was used to detect significant differences. Results: We found significant positive correlations between PRRT outcome and baseline Hb, erythrocytes and lymphocytes, which is compatible with a cascade of free radical damage followed by immune activation. We found an inverse correlation between PRRT outcome and baseline neutrophils. No correlation between PRRT outcome and leukocytes or platelets was found. Conclusion: Our results suggest that optimization of hemoglobin content prior to PRRT may be beneficial for therapy efficacy. Keywords: prrt, hematology, prognosis, 177lu-dotatoc
Peptide Receptor Radionuclide Therapy (PRRT) for Treatment of Functional and Metastatic Phaeochromocytoma (PCC) and Paraganglioma (PGL)

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Introduction: Treatment options for metastatic PCC/PGL and related hypertension (HTN) are limited. Experiences in PRRT suggest favourable disease control, but lack of data on HTN response. **Aim(s):** We assessed PRRT outcomes in patients (pts) with high somatostatin receptor (SSTR) expression from 2 referral centres. **Materials and methods:** 16 pts (M:F=11:5; 21-77 y.o) treated with 177Lu-DOTA-octreotate were retrospectively reviewed. Median cumulative activity 21.5 GBq, most had 4 cycles, 7 had radiosensitising chemotherapy. 4 pts had SDHB mutation, 1 SDHD, 2 negative and 9 unknown. 12 pts were treated for secondary HTN and 4 pts for non-functional metastatic disease/recurrence. **Results:** 6/12 pts had HTN improvement with reduction of anti-HTN medications at 3 months post PRRT, 5 had HTN stabilisation, 1 pt lost to follow-up. 89% had serum chromogranin-A reduction. For all pts cohort, 40% had disease regression (30% partial, 10% minor response) on CT, and stable findings in 40%. 2 pts had bony disease evaluable only on SSTR imaging (1 partial response, 1 stable). 4 pts died, median overall survival not reached, median follow-up 43.5 months. 2 pts had Grade3 lymphopenia, 1 Grade3 thrombocytopenia, with no significant renal toxicity. **Conclusion:** In addition to favourable disease control and minimal toxicity from PRRT, our results also indicate potential clinical and biochemical effectiveness in pts with functional metastatic SSTR+ PCC/PGL. Prospective PRRT trials are warranted for this population with complex clinical and tumour heterogeneity. **Keywords:** prrt
Peptide Receptor Radionuclide Therapy (PRRT) with a Somatostatin Receptor (SSTR) Antagonist in Patients with SSTR-Positive, Progressive Neuroendocrine Tumours (NETs): A Phase I/II Open-Label Trial to Evaluate the Safety and Preliminary Efficacy of 177Lu-OPS201

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Introduction: PRRT with radiolabelled SSTR agonists is highly effective and has become an integral part of NET treatment. Tumour uptake and tumour-to-tissue dose ratios may be higher with radiolabelled SSTR antagonists than agonists. DOTA-JR11 (OPS201) is a very promising next-generation SSTR2-selective antagonist. Aim(s): This phase I/II, international, single-arm, open-label study will evaluate 177Lu-OPS201 as PRRT in 45 adults with unresectable, SSTR-positive, progressive gastroenteropancreatic-NETs, lung NETs, phaeochromocytomas and paragangliomas. Materials and methods: Phase A: 6 patients receive 3 cycles of 177Lu OPS201 at 4.5 GBq over 24 weeks. A further 9 patients receive 3 cycles of 177Lu OPS201 at 4.5 GBq, or an activity not evoking dose-limiting toxicity, dependent on initial safety/dosimetry data. Phase B: 30 patients receive 3 cycles of 177Lu OPS201 at up to 7.4 GBq, dependent on phase A safety/dosimetry data. Tumour response (centrally reviewed [RECIST1.1]) will be assessed on CT/MRI every 3 months from end of core trial visit for 2 years, or until progressive disease/death. Results: Primary endpoint is safety/tolerability. Secondary endpoints: biodistribution and pharmacokinetics (maximal uptake, area-under-curve, terminal half-life); radiation dosimetry; preliminary efficacy (tumour response, progression-free survival), and quality of life. Conclusion: This study evaluating safety and efficacy of 177Lu-OPS201 as PRRT is planned to start in Jan 2017 (NCT02592707; EudraCT 2015-002867-41). Industry sponsored. Keywords: prrt, 177lu, ops201
Survival Analysis after i.a. 90Y-DOTATATE PRRT, in Patients with Non-Resectable, Advanced, Progressive, Liver-Dominant Neuroendocrine Neoplasms

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Introduction: A Aim(s): To assess long-term survival in non-resectable, progressive, liver-dominant GEP-NEN after intraarterial (i.a.) 90Y DOTATATE peptide receptor radionuclide therapy-PRRT Materials and methods: 22 subjects, 12 female, mean age 56.2. Histological proven G1/G2/G3: 4/17/1; secretor 10 pts (46%). Documented progression DP: 100% (RECIST, clinical or biochemical in case or secretor tumors) with relapse on previous therapy. Overall 56 i.a. 90Y-DOTATATE sessions. Initial tumor responses assessed, 6wks after PRRT and then 3mo intervals of follow-up. Objective tumor response was classified according to RECIST 1.0, initially 6wks and then after each of the 6mo. OS and PFS were evaluated using Kaplan Meier methods Results: OS for all pts: 52.0mo PFS 25mo. The clinical response based on performance status (PS), WHO initial and 6 wks after PRRT improved (P<0.05). In pts with initial clinical response after 6 wks, OS was 63.0mo when PS =0, and was 44 mo in those with PS>0 (P<0.05). No difference was noted in OS for gender (M-52, F-52.5 mo), secretor vs. non (47.0/61.0 mo) and G1/G2 (41/53 mo). Clinical response at 6wks: PR-5, SD-17 and PD-2. At 6mo PR-17, SD-3 and PD-2. After 12mo PR-15, SD-2 and PD-3. After 24mo PR-8, SD-8 and PD-3. RECIST response at 6wks: PR-2, SD-19; at 6mo: PR-4, SD-15 and PD-2. At 12mo, PR 4, SD 15 and PD 1. After 24mo, PR-3, SD-12 and PD-2 Conclusion: i.a.PRRRT is effective in patients with extensive,liver dominant,non-resectable and progressive GEP-NENs Keywords: intra-arterial prrt, progressive gep-nens, liver dominant

(N13)
The Effect of PRRT on Health-Related Quality of Life in NET Patients: A Prospective Study

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Introduction: Neuroendocrine tumour (NET) patients experience poor health-related quality of life (HRQOL). Peptide receptor radionuclide therapy (PRRT) is a promising treatment option although its impact on HRQOL is not well understood. Aim(s): This prospective observational study examined the time course of HRQOL in a cohort of patients at the Department of Nuclear Medicine The Queen Elizabeth Hospital, Adelaide. Materials and methods: Patients received up to 4 Lutate inductions at 6-8-weekly intervals. The EORTC QLQ-C30 was administered prospectively at baseline and before each cycle. Mixed models for repeated measures examined relationships between time and HRQOL. Results: Participants were 71 NET patients (49.3% female). Mean age was 62.74±13.49 years. QLQ-C30 data was available for 88.7%, 77.5%, 69.0% and 67.6% of patients at baseline and inductions 2-4, respectively. The reasons for missing data include drop out, non-compliance and older age. There were significant improvements in QLQC30 global QOL (estimate = -9.15, 95%CI -15.67, -2.64), social functioning (est = -10.99, 95%CI -18.11, -3.86), emotional functioning (est = -4.60, 95%CI -8.38, -0.83), appetite loss (est = 10.73, 95%CI 1.91, 19.53), and diarrhoea (est = 7.66, 95%CI 0.52, 14.81) from baseline to time 4. There was an effect of time on global QOL, role functioning, social functioning, nausea/vomiting, pain, and dyspnoea (p<0.05) but not on fatigue. Conclusion: PRRT for progressive metastatic NETs is associated with improvements in HRQOL. Keywords: prrt, quality of life, lutate
(N15)
Lanreotide Autogel/Depot (LAN) in Combination with Peptide Receptor Radionuclide Therapy (PRRT) in Progressive Digestive and Lung Neuroendocrine Tumours (NETs): Design of the PRELUDE Study

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Introduction: PRRT has potential to control progressive NETs and has been used in combination with somatostatin analogues such as LAN. Aim(s): To investigate effects of PRRT in combination with LAN (LAN–PRRT) in pts with progressive gastroenteropancreatic (GEP) - and lung NETs. Materials and methods: This retrospective study will analyse existing records to describe LAN–PRRT in 150 pts from 5 countries (NCT02788578). Key inclusion criteria are adults with progressive, metastatic well-differentiated GEP- or lung NETs, evaluable imaging ≤6mo and ≤12mo before first LAN–PRRT cycle and at end of last cycle, positive SSTR status, ECOG PS0–1, ≥1 LAN injection in 8wks prior to first LAN–PRRT cycle, no prior PRRT, continuous LAN in all cycles, and total cumulative activity of ≥500mCi of 177Lu-DOTATOC or 177Lu-DOTATATE. Results: Primary endpoint is PFS rate at end of last LAN–PRRT cycle (RECIST v1.1, central reading). Secondary endpoints include: PFS at last available follow-up visit (≤12mo); best overall response; objective response rate after last cycle and at last follow-up; changes from baseline (day 1 of first LAN–PRRT cycle) to last cycle, and last follow-up in frequency/severity of diarrhoea and flush; change in CgA level and body weight; and incidence of nephro-, haemato- and hepatotoxicities, and vomiting during infusion. Conclusion: PRELUDE will assess LAN–PRRT effectiveness and tolerability in a sizable cohort of patients with progressive GEP- and lung NETs. Recruitment is active. Industry sponsored. Keywords: prrt, lanreotide
Treatment of Paragangliomas with Lutetium-177-Octreotate Based Peptide Receptor Radionuclide Therapy

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Introduction: Paragangliomas (PGL) are a heterogeneous group of rare tumours that can express high numbers of somatostatin receptors on their cell surface and can be targeted with peptide receptor radionuclide therapy (PRRT) using the radiolabelled somatostatin analogue [lutetium-177-DOTA-Tyr3]-octreotate (177Lu-octreotate). Aim(s): To report safety and efficacy. Materials and methods: From a larger cohort treated with PRRT, all Dutch patients with histologically proven inoperable or metastatic PGL were selected. The intended dose of 177Lu-octreotate was 4x 7.4 GBq, administered with intervals of 6-12 weeks. Data were prospectively registered, Kaplan-Meier analysis was used to express survival. Results: Eleven patients with extra-adrenal (EA) and 17 with head and neck (HN) PGL received a total of 104 administrations. No severe (sub-)acute bone marrow or kidney toxicity was observed. A subacute, mild adverse event due to catecholamine release occurred in one patient. Best tumour response (RECIST 1.1) was partial response in 6 (21%), stable disease in 18 (64%) and progressive disease in 4 (14%) patients. With 12 patients experiencing progressive disease at baseline, an objective response was observed in 10/28 (36%). Median progression free survival was 30 months for all patients; 14 in EA-PGLs versus not reached in HN-PGL (median follow-up 49 months). Conclusion: This study shows that PRRT is a safe and effective treatment for inoperable or metastatic PGL, and supports the implementation of PRRT into the treatment algorithm. Keywords: prrt, paragangliomas
A Nuclear Combination in Heterogeneous Metastatic Neuroendocrine Tumors

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Introduction: Therapy with 177Lu-DOTATATE provides an objective response in neuroendocrine tumors (NET). Aim(s): A clinical case of a metastatic NET with different grades of differentiation treated with PRRT and chemotherapy is presented. Materials and methods: Clinical data were reviewed. Results: A 42yr old woman, ECOGPS0, was evaluated for right hypochondrium pain. Abdominal US and CT showed a pancreatic lesion and liver nodules. Biopsies revealed a low grade pancreatic NET (Ki67 <2%) with high grade liver metastases (Ki67 20%). For staging 68Ga-DOTANOC and 18F-FDG PET-CT were performed. 68Ga-DOTANOC was positive in pancreatic lesion and some liver metastases, showing nodal and vertebrae metastasis. 18F-FDG PET-CT was positive in some liver metastases. First line therapy with lanreotide, capecitabine and temozolamide was proposed. After three months, CT showed partial morphological response. Therapy with 177Lu-DOTATATE (~203mCi/cycle) and capecitabine (1300mg 2id) was suggested. Toxicity was evaluated after each cycle. The patient has completed 3cycles. After 3rd cycle, 18F-FDG PET-CT showed a complete metabolic response (100%) and 68Ga-DOTANOC PET-CT a partial response in liver (28%), pancreas (78%), lymph node (4%) and bone lesions (5%). No toxicity was reported except a grade 2 hematological toxicity after 3rd cycle. Conclusion: This case documents the importance of 18F-FDG and 68Ga-DOTANOC PET-CT in staging these heterogeneous tumors. No significant toxicity and a good response were observed after PRRT and chemotherapy. Keywords: prrt, 68ga-dotanoc
Peptide Receptor Radionuclide Therapy in a Patient with SDHB Related Grade 3 Paraganglioma (PGL) of Urinary Bladder

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Introduction: SDHB mutation cause aggressive metastatic PGL. 36% of patients survive 5 yrs, treatment options are limited & many still being evaluated. Aim(s): 1st case of SDHB bladder PGL treated with Lu-177 DOTATATE

Materials and methods: Review presentation, biochemistry, histology, imaging, therapy effect & survival

Results: Presentation: vague abdominal pain 09/2014. Resected bladder mass showed aggressive PGL, Ki 67 35%. Bone & MIBG scans underestimated disease. Gallium 68 DOTANOC & FDG PET CT were matched & accurately staged patient 02/2015. 4 cycles 7.4 GBq Lu-177 DOTATATE administered 02/2015 - 11/2015. Post therapy images showed no progression, however Normetanephrine level remained increased (baseline 3434, post therapy 3832 nmol/24 hrs). Other tumour markers normalized. Therapy caused mild grade 1 hematotoxicity, patient remained asymptomatic. Imaging 3 months after the 4th cycle (02/16) showed rapid progression, in 07/2016 Chromogranin A 2905 ng/ml, 24 hr urine Normetanephrine 51105 nmol/24 hrs and Urine Normetanephrine:Creatinine ratio 978.6 nmol. Patient became symptomatic (hypertension & left hydronephrosis). Salvage therapy 7.4 GBq Lu-177 DOTATATE administered 10/2016. This caused BP spikes up to 200/110 mmHg. Post therapy scan showed diffuse bone marrow infiltration & platelets decreased from 198 to 81 ×10E12/L

Conclusion: Patient alive 27 months. Initial PRRT well tolerated with no progression on post therapy images. Salvage PRRT caused catecholamine increase & grade 3 hematotoxicity. PRRT can be considered in G3 bladder PGL if SSR avid

Keywords: sdhb, bladder pgl, prrt
NETTER-1 Phase III Trial: Recent Findings on Quality of Life in Patients with Midgut Neuroendocrine Tumors


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Introduction: Impairment in quality of life caused by tumor load and hormone-related symptoms is frequent in GEP-NET patients. In the Phase III NETTER-1 trial, patients with advanced, progressive midgut NETs were randomized to treatment with 177Lu-DOTATATE (177Lu; Lutathera®) or high-dose (60 mg) Octreotide LAR (Oct). Aim(s): EORTC questionnaires C30 and GINET21 were used to determine the impact of treatment on health-related quality of life (HRQoL). Materials and methods: Patients completed the two QoL questionnaires at baseline and every 12 weeks until disease progression. Individual changes from baseline scores were assessed. Deteriorations/improvements were considered clinically significant when ≥10 points. Results: Clinically and statistically significant improvements in QoL were observed in the 177Lu arm versus the Oct arm at certain time points in key domains of HRQoL including global health status and diarrhea. In mean, global health status improved in 28% of 177Lu patients (15% on Oct) and worsened in 18% (26% on Oct). Diarrhea improved in 39% of 177Lu patients (23% on Oct) and worsened in 19% (23% on Oct). Flushing/sweats improved in 42% of 177Lu patients (38% on Oct) and worsened in 22% (19% on Oct). A benefit was suggested in pain that was not statistically significant. Conclusion: Treatment with 177Lu-DOTATATE improves certain QoL and NET symptom scores in a clinically and statistically significant fashion compared to high-dose octreotide in patients with advanced midgut NETs. Keywords: 177Lu-dotatate, prrt, net, quality of life
Survival Analysis of Combined Therapy with 177Lu-Octreotate and Somatostatin Analogues in Advanced Metastatic Neuroendocrine Tumours

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Introduction: Although somatostatin analogues (SSA) and peptide receptor radionuclide therapy with 177Lu-octreotate (PRRT) are validated therapies in patients with advanced metastatic neuroendocrine tumours, it is still unclear if the combined therapy with PRRT and SSA can provide a prolonged survival compared to patients treated with PRRT alone. Aim(s): The aim of our study was to investigate if there is a survival benefit from the combined therapy.

Materials and methods: The investigation included 225 patients with progressive gastroenteropancreatic neuroendocrine tumours. 98 of the patients received a combined therapy with PRRT and SSA, 127 patients had a PRRT monotherapy. For the survival analysis the minimal follow-up was 6 months. Results: Data for overall survival (OS) was available from 122 patients and from 113 patients for the progression free survival (PFS), respectively. We identified two subgroups of patients, which showed a survival benefit from the combined therapy. The first group were tumours with Ki67 > 10%, which achieved with the combined therapy a prolonged OS (median, 27.5 vs. 18 months) and PFS (median, 23.5 vs 13.5 months). The second group were patients with high tumour burden: > 10 metastases or chromogranin A > 600 ng/mL or liver involvement > 50%. Both OS (median, 45 vs. 34 months) and PFS (median, 29 vs. 21 months) were longer with a combined therapy. Conclusion: Patients with Ki67 > 10% or high tumour burden showed a survival benefit from the combined therapy (PRRT + SSA).

Keywords: prrt, ssa, combined therapy, survival
Study Protocol: Prospective, Randomized Controlled Trial on the Effect of Primary Resection in Advanced Metastatic NEN of Pancreas and Midgut (PRESNENAS)

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Introduction: The role of Primary Tumor resection in advanced metastatic NEN is discussed controversially. Aim(s): To show the benefit of primary resection on progression-free survival in advanced metastatic pancreatic and midgut NET (Stage IV) compared to biotherapy Materials and methods: Well differentiated neuroendocrine neoplasia (NET, G1, G2, Ki-67<10\%) of midgut and pancreas with surgically non-resectable metastases and asymptomatic, resectable primary tumor. Comparison between surgical primary resection plus biotherapy and biotherapy only. Results: A study protocol was developed and presented at national meetings showing a good acceptance and eligibility of the protocol. We expect 450 pts. to assess for eligibility, 370 for study entry. Calculated median progression free survival times are 16 months (control group, biotherapy only) and 23,2 months (intervention group, primary resection + biotherapy) resulting in a hazard ratio of 0.690. Conclusion: We present a detailed study protocol: Prospective, randomized controlled trial on the effect of primary resection on progression free survival in well differentiated, advanced metastatic neuroendocrine neoplasia of pancreas and midgut with asymptomatic primary tumors (PRESNENAS). Financial calculation was done with the intent to apply support of the DFG. 25 Centers should participate with 5 patients to enrol per year. Duration of the entire trial is planned with 72 and recruitment period with 36 month. Keywords: prospective randomized, controlled trial, surgery, role of primary resection

Neuroendocrinology 2017;105(suppl 1): 1-338
Comparison of Long Terms Outcomes after Resection of Hepatic and/or Peritoneal Metastasis from Neuroendocrine Tumors

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Introduction: The complete resection of liver metastasis LM is usually recommended in patients with grade 1-2 NET. The exact benefit of resection of peritoneal metastasis PM is unknown. Aim(s): To compare the long-term survivals of patients operated on form LM and/or PM from NET. Materials and methods: All pts operated on from Jan. 2005 and Dec.2015 were included. We analyzed 3 groups of resection: LM only, PM only and combined LM + PM. Surgical indications were discussed in a multidisciplinary meeting and performed exclusively if a complete macroscopic resection could be achieve. Results: In total 71 its were included in the LM group, 22 in the PM group and 35 in the combined LM + PM group. Primary tumor originated from the small bowel origin in most cases (28% LM, 50% PM, 80% LM +PM groups). For patients with LM, surgery consisted in hepatic resection associated with radiofrequency ablation in most cases (79% LM, 65% LM + MP). The mean number of resected LM was 8 [1-50] in the LM group and 9 [1-55] in the LM + PM group. For patients with PM the mean peritoneal cancer index was 10 [4-26] in the CP vs. 11 [4-28] in the LM + PM group. At 5-year, OS was similar between groups (respectively 83%, 83%, 80% in groups LM, PM, an LM + PM) (log-rank p=0.1). The 2-years DFS was also comparable (39% in LM group and 31% in PM and LM + PM groups). Conclusion: This study suggests that the surgical resection of PM offers prolonged survival in these selected population. Keywords: liver metastasis, peritoneal metastasis, surgery
Trans-Anal Minimally Invasive Surgery (TAMIS) for Completion Local Excision of Well-Differentiated Rectal Neuroendocrine Tumours

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Introduction: Rectal NETs (R-NETs) <2cm are often amenable to endoscopic resection, but initial resections are often incomplete, and extended monitoring or radical surgery may then be required. Trans-anal minimally invasive surgery (TAMIS) allows resection of rectal tumours while reducing surgical morbidity. Data on its use in R-NETs is scant. Aim(s): To assess the results of TAMIS for completion local excision of R-NETs following endoscopic resection.

Materials and methods: We reviewed patients undergoing TAMIS for NET at our institution (2013-2016). Included patients had incomplete endoscopic resection (margin ≤1mm), a visible scar on repeat endoscopy, and localized disease on systemic imaging. Full-thickness resection of the endoscopic scar was performed. Outcomes were 30-day major morbidity (Clavien-Dindo III-V), resection margin, and oncological outcomes.

Results: Of fourteen patients included, 12 had G1 R-NET and 2 unknown grade. Median distance from the anal verge was 7 (range 5-13) cm. Median operating time was 41.5 (range 20-79) minutes. No major morbidity was documented. Viable tumour was found in 3 specimens, all Grade 1 with negative margins. At 17 months median follow-up, all patients were alive and asymptomatic, with no change in sphincter function and no evidence of local recurrence.

Conclusion: TAMIS is a safe and feasible approach for well-differentiated R-NETs to clear margins following incomplete endoscopic resection. It limits invasiveness of intervention and avoids time-consuming monitoring after incomplete resection.

Keywords: tamis
Conditional Survival (CS) Analysis of Liver Resection (LR) for Gastro-Entero-Pancreatic Neuroendocrine Tumor (GEP-NET)

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Introduction: LR with curative intent in metastatic GEP-NET is rarely feasible associated with improved survival and symptoms control. CS is the probability that pts will survive an additional number of yrs given that they have already survived at a certain interval. Aim(s): There is no study on CS in pts undergoing GEP-NET LR. Materials and methods: 87 pts with GEP-NET liver mets underwent LR with curative intent (1995-2015). Cox proportional hazard regression model was applied to evaluate OS, TTR and associated prognostic factors. 3-year CS estimates at ‘t’ yrs after LR were calculated as: $CS(t) = S(t + 3)/S(t)$ Results: Median follow-up was 104 months and median survival 256 months. 1, 3, 5, and 10-year OS rates were: 91%, 89%, 83% and 69%, respectively. Significant adverse prognosis was in presence of carcinoid symptoms (p: 0.040), G3 (p: <0.001), MIB-1 >5% (p: <0.001) and early (<36 months) recurrence (p: <0.001). Recurrence rate was 53% (46/87 pts) with a median TTR of 53 months. The probability of surviving an additional 3 yrs at 3, 5 and 10 yrs after LR were 86.5%, 90.4% and 73.9%, respectively (NS). Prognostic factors related to biology prevailed in early recurrences with no impact in late recurrences and late CS Conclusion: LR for GEP-NET is associated with prolonged survival. Biological prognostic factors (grading and MIB-1) influence survival independently. CS provides important information about dynamic prognostic changes over time for GEP-NET liver mets and may help in planning adjuvant strategies. Keywords: survival, liver resection, gep-net
La paroscopic and Robotic Resection for Pancreatic Neuroendocrine Tumors (pNET): Less Is More?

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Introduction: Laparoscopy is useful for the resection of pNET, but only a few studies in the Literature describes outcomes for a large series. Aim(s): To describe perioperative and oncologic outcomes of a single center minimally invasive resected pNET series. Materials and methods: We analyzed the consecutive series of Patients undergoing laparoscopic/robotic surgery for pNET from January 2002 to October 2016 at the Verona Pancreas Institute. Results: During the study period 97 Patients (54% female) underwent a minimally invasive resection for pNET; median age was 56 years, median BMI 25.8 Kg/m². We performed 51 distal pancreatectomies with splenectomy (10 robotic, RA), 25 spleen-preserving distal pancreatectomies (8 RA), 19 enucleations (4 RA), 2 laparoscopic middle-pancreatectomies. We had a 215 minutes median operative time, 11 (11.3%) conversions to open; mortality was null. 37 Patients had an uneventful course, incidence of clinically relevant POPF was 23.7%, incidence of bleeding was 8.2%. 10 Patients were reoperated on, abdominal abscess was the most frequent indication and laparoscopic the preferable approach. Median hospital stay was 7 days. 10 Patients were readmitted. Mean tumor size was 23 mm (4-100). Mean number of lymph-node harvested was 11 (0-37). Conclusion: Laparoscopic and robotic approach are safe and effectiveness techniques and considering their advantages over open surgery, they should be proposed at the population of Patients affected by pNET selected for a targeted surgical resection. Keywords: laparoscopic robotic surgery
Resection of Liver Metastases in Patients with High-Grade Gastroenteropancreatic Neuroendocrine Carcinomas: A Nordic Multicenter Study


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Introduction: Gastroenteropancreatic neuroendocrine carcinomas (GEP-NEC) are generally characterized by synchronous metastases, high aggressiveness and a dismal prognosis. Currently, resection of liver metastases in patients with metastatic GEP-NEC is not recommended. However, the existing data are scarce. Aim(s): The aim of this study was to evaluate the role of liver surgery as part of the treatment in metastatic GEP-NEC. Materials and methods: 32 patients with a diagnosis of GEP-NEC (Ki-67 >20%) who had intended curative resection of liver metastases, were identified among 840 patients from two Nordic GEP-NEC registries. Tumor morphology was reassessed. Overall survival (OS) and progression-free survival (PFS) was assessed by Kaplan-Meier analyses for the entire cohort and for subgroups. Results: Median OS after resection of liver metastases was 35.9 months (95%-CI: 20.6–51.3) with a five-year OS of 43%. Median PFS was 8.4 months (95%-CI: 3.9-13), with a five-year PFS of 13%. Two of 32 patients had well-differentiated morphology and 20 patients had Ki-67≥55%. A Ki-67<55% and treatment with postoperative chemotherapy were statistically significant factors of improved OS after liver resection. Conclusion: Our results show a long survival after liver surgery for many metastatic GEP-NEC patients, particularly for the group with Ki-67: 21-55%. Resection of liver metastases may be considered for selected GEP-NEC patients and should probably be followed by chemotherapy. Keywords: neuroendocrine carcinoma, liver metastasis, liver surgery, ki67, survival
Should Surgery Be Conducted for Small Nonfunctioning Pancreatic Neuroendocrine Tumors: A Systemic Review

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Introduction: Researches showed controversial results regarding whether surgery should be conducted for nonfunctioning pancreatic neuroendocrine tumors (PNETS) smaller than 2 cm. Both the ENETS and NCCN guidelines recommended observation for selected cases, while none of them pointed out which cases should be chosen. Aim(s): To find out whether PNETS smaller than 2 cm need surgery and which subgroup would benefit the most from surgery. Materials and methods: MEDLINE, EMBASE and CENTRAL were searched until 2016/08/30, with primary outcome being overall survival, and secondary outcome being progression free survival, disease specific survival and disease recurrence/progression. Results: 3 cohort studies and 5 case series were selected for analysis. Patients who meet the following two requirements were suitable candidates for observation: 1) No signs of local invasion, nodal metastasis and distant metastasis on high-quality imaging studies; 2) Favorable histological findings with Ki-67 < 5% or Ki-67 < 2% at best. Since definite pathological results could not be achieved before operation, a preoperative predictive system for malignancy is necessary. We identified 4 factors that were statistically significant: tumor > 1 cm, age > 55, Asian/Black race and elevated CgA level. These factors may be included in a nomogram model to predict malignancy. Conclusion: Several factors can help us estimate malignant potential of small PNETS and a more accurate predictive system is required to aid decision making for surgery. Keywords: pnets, 2 cm, surgery
Systematic Review of Resecting Primary Tumor in MNETs Patients with Unresectable Liver Metastases

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Introduction: Treatment for midgut neuroendocrine tumors (MNETS) with unresectable liver metastasis has long been a controversial issue. Aim(s): This system review aims to summarize existing evidence concerning the value of primary tumor resection for MNETS with unresectable liver metastasis. Materials and methods: MEDLINE, EMBASE and CENTRAL were searched until 2016/07/04 for relevant studies, with primary outcome being overall survival, and secondary outcome being progression free survival, cause of death and symptom relief. Results: 8 cohort studies were identified for qualitative analysis. None of them strictly met with the inclusion criteria and meta-analysis was impossible. There was a tendency towards better overall survival for the primary tumor resected group in all 8 studies, in which 6 demonstrated significant difference. Progression free survival to liver disease was prolonged and less patients died of liver failure in the resected group. There were also evidences showing that primary tumor resection could reduce death caused by primary tumor burden and carcinoid syndrome. Conclusion: Current evidence supports resection of primary tumor for midgut neuroendocrine tumor patients with liver metastases, but randomized controlled trials are required to reach a final conclusion. Keywords: midgut neuroendocrine tumor, liver metastasis, primary tumor resection
Patient Outcomes after Cardiac Surgery for Carcinoid Heart Disease Are Dependant Upon Successful Cytoreductive Multimodal Treatment and Control of Metastatic Neuroendocrine Disease

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Introduction: Carcinoid Heart Disease (CHD) as a result of long standing carcinoid syndrome is associated with a poor prognosis due to development of valvular incompetence & right heart failure. Cardiac valve surgery is the main therapeutic option. Aim(s): To assess the long term outcomes of patient undergoing valve surgery as part of a multimodal cytoreductive treatment strategy for metastatic NET. Materials and methods: Review of patients presenting to the regional NET multidisciplinary meeting over a 5-year period who underwent valve surgery for CHD. Results: 11 patients (9 female), median age 62 years. Commonest tumour site was small bowel(10), 9 patients had metastatic liver disease. Tumour grade 1(8), grade 2(3). Urinary 5HIAA (median 795, range 187-2690) & serum chromogranin A (median 1015, range 229-4047) were elevated in all patients and decreased to median 267 & 355 respectively after cytoreductive treatment. Median time from diagnosis CHD to surgery was 15(range 3-144) months. All patients had tissue valve replacement & underwent additional multi-modality treatments. At median follow-up 9(range 3-65) months, there were 4 early deaths at 3,4,4&12 months from cardiac failure from progressive (3) or untreated (1) disease. Of remaining patients, at median follow-up 23(range 4-56) months, 6 of 7 have completed treatment and have stable disease. Conclusion: Good outcomes are achievable in patients after valve surgery who have undergone successful cytoreductive treatment leading to disease control. Keywords: carcinoid heart disease, surgery
Primary Tumor Resection Results in Superior Overall Survival after Peptide Receptor Radionuclide Therapy in Advanced Neuroendocrine Neoplasms

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Introduction: Peptide receptor radionuclide therapy (PRRT) is an highly effective therapeutic option to treat advanced neuroendocrine neoplasms (NEN). However, it is still unclear whether resection of primary tumors improves overall survival (OS) after PRRT. Aim(s): To find out whether resection of primary tumors prior to PRRT will result in better overall survival than without. Materials and methods: Retrospectively, we analyzed the data of 1048 patients with advanced NEN treated with PRRT. In 541/1045 patients (52%, group 1) primary tumors were removed. Group 2 enfolded 444 patients (42%) with no resection previously, no data: 60 patients (6%). Progression free survival (PFS) was determined by 68Ga SSTR-PET/CT and EORTC response criteria. Results: Most patients had their primary tumor in pancreas (n = 384; 37%) and small intestine (n = 315; 30%). Patients received a combined treatment with 90Yttrium and 177Lutetium cycles (513; 49%), only 177Lutetium (378;36%) and only 90Yttrium (157; 15%), exclusively. OS in group 1: was 98.4 months (CI: 93.0 -103.9), whereas OS in group 2: was 61.9 months (CI: 57.1 – 66.6); p < 0.001. Likewise, PFS was extended after PRRT in group 1: 24.1 months (CI: 22.2 – 26.0) versus group 2: 18.4 months (CI: 16.8 – 20.0); p< 0.001. Conclusion: After surgery of primary tumors, patients have a better overall survival and progression free survival after PRRT. These effects may result from selection bias, however, they are strong indicators for clinical practice that primaries should be removed when feasible. Keywords: prrt, surgery
Selective Approach in Surgical Treatment of Pancreatic Neuroendocrine Tumors

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Introduction: Surgical resection is the main method in treating of pancreatic neuroendocrine tumors (pNETs). Contemporary perioperative diagnostic can help using selective approaches, to perform organ-preserving (OP) procedures including operations with miniinvasive techniques (MI) such as robot – assisted (RA) or laparoscopic (La). Aim(s): To improve results of pNETs treatment Materials and methods: We made a retrospective analysis of treating of 92 patients with pNETs. Most of them were female 67 (73%), average age 51.2±12.9. There were 52 (56.5%) patients with functional pNETs. Results: 52 procedures with conventional laparotomy and 36 (33 RA, 3 - La) were performed in our department. MI procedures were performed in cases when tumor was less than 30 mm. OP procedures were made in cases with G1 pNETs. Distal pancreatectomies were performed in 36 cases (21 – conventional, 13 – RA, 2 La). Pancreaticoduodenectomies were made in 23 cases (20 conventional, 3 – RA); there were 21 tumor enucleations (8 – traditional, 12 RA, 1 - La), 9 central resections (4 traditional, 5- RA) and 3 total pancreatectomies (all of them were performed by conventional laparotomy).

Conclusion: Surgical treatment of pNETs requires selective approach in choosing of volume technique of resection. In cases of G1 pNETs - OP procedures have to be performed. Contemporary perioperative diagnostic can reduce volume of removing pancreatic tissue allows to perform OP operations.

Keywords: pancreatic neuroendocrine tumors, surgical treatment, robot, assisted, miniinvasive, laparoscopic
(O12)
Prognostic Factors for Long-Term Survival in 102 Consecutive Pancreatic Resections for Primary Neuroendocrine Tumor

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Introduction: Neuroendocrine tumors (NET) of the pancreas represent a rare entity of primary pancreatic tumors. However, with the continuous progress in modern diagnostics NET’s are increasingly detected and prognostic factors are being reevaluated to establish personalized treatment concepts. Aim(s): The aim of this study was to analyze our patient population with regard to surgical outcome and overall survival. Materials and methods: 102 consecutive patients who underwent pancreatic resection for primary pancreatic NET at our institution were analyzed for surgical outcome and radicality as well as for tumor size, Ki-67 and MIB-1 status. Results: The tumor was hormone-active in 19 patients (19%) and hormone-inactive in 81 patients (79%). 2 patients had a MEN-1 syndrome. Pancreatic head resection was performed in 53 patients (52%), distal pancreatectomy in 45 patients (44%), total pancreatectomy in 3 patients (3%) and local tumor enucleation in 1 patient (1%). Postoperative pancreatic fistula and hemorrhage occurred in 10 (10%) and 11 patients (11%) respectively whereas postoperative mortality occurred in 1 patient. A margin-free resection status ($p = 0.00$) and a low growth fraction ($p = 0.03$) were identified as positive predictive markers for long-term survival. Conclusion: Pancreatic resection for primary NET’s may be performed safely with promising long-term results. Surgical therapy may thus be considered as an important treatment option in the interdisciplinary treatment of patients with pancreatic NET’s. Keywords: net, pancreas, surgery
18F-FDG Positron Emission Tomography/Computed Tomography Positivity in Small Incidentally-Found Pancreatic Neuroendocrine Tumors: Could It Be Considered a Predictor of Malignancy?

Malpaga A, Impellizzeri H, Damoli I, Miotto M, Paiella S, Amodio A, Bianchi B, Crepaz L, Marchegiani G, Ortolani S, Regi P, Butturini G, Salgarello M, Cingarlini S, Landoni L; A Department of Surgery, Pancreas Institute, Verona, Italy B Department of Gastroenterology, Pancreas Institute, Verona, Italy C Department of Oncology, C.C Pederzoli, Peschiera del Garda, Italy D Department of Surgery, C.C Pederzoli, Peschiera del Garda, Italy E Department of Nuclear Medicine, Ospedale Sacro Cuore, Negrar, Italy F Department of Oncology, Pancreas Institute, Verona, Italy

Introduction: Surgical management of small (<2 cm), incidentally found sporadic non functioning pancreatic neuroendocrine tumors (NF-PanNETs) is controversial. Normal practice in our Institution is to observe them when asymptomatic, without worrying features at imaging and without uptake at F-PET/CT. Aim(s): To evaluate the impact of positive F-PET/CT findings in NF-PanNET < 2cm Materials and methods: Data of patients submitted to pancreatic resection for PanNET from 2010 to 2016 at the Authors Institution were retrospectively reviewed (n=268). We selected incidentally found NF-PanNET < 2 cm, with pre-operative F-PET/CT positivity Results: 7 cases (5 F/2 M), with a median age of 58,9 years (range 33-83) were found. SUV max at F-PET/CT, when reported, was various (range 12-35). 2 patients underwent pancreaticoduodenectomy, 3 distal pancreatectomy, 1 enucleation, 1 middle pancreatectomy. The median tumor size was 15,7 mm (range 8-20). 3 tumors were G1, 4 were G2 (Ki67 max 7%); lymph node metastases were found in 2 patients (1 G1 and 1 G2); microscopic vascular invasion was reported in one case (G2, N1). At a median follow-up of 35,6 months, no patients develop recurrence Conclusion: 4 out of 7 tumors with pre-operative F-PET/CT positivity had features of uncertain behavior (G2, N1, microscopic invasion). The impact of F-PET/CT positivity in characterizing small (<2 cm) occasionally found NF-PanNET is not almost clear, but it should be take into account in the diagnostic workup Keywords: f-pet/ct positivity, small pan net
Are Cystic Pancreatic Neuroendocrine Tumors an Indolent Entity?
Results for a Single Institutional Surgical Series

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Introduction: Cystic pancreatic neuroendocrine tumors (CPanNET) are an uncommon variant of pancreatic neuroendocrine tumors (PanNETs). Due to their rarity, there is a lack of knowledge with regards to clinical features and prognosis. Aim(s): Better define this entity Materials and methods: The prospectively maintained database of a high-volume Institution was queried and 46 resected CPanNETs were detected from 1995 to 2015. Clinical and pathological features and survival outcomes of CPanNET were described and matched with a population of 92 solid PanNETs (SPanNETs) for comparison Results: CPanNETs accounted for the 7.8% of the overall number of resected PanNETs (46/587). CPanNETs were mostly sporadic (n=42, 91%) and non-functioning (n=39%). Two functioning CPanNETs (gastrinomas, 4.3%) were detected (4.3%). The median tumor diameter was 30 mm (range 10-120). All tumors were well differentiated, with 38 (82.6%) G1 and 8 (17.4%) G2 tumors. Overall, no CPanNET showed a Ki-67>5%. A correct preoperative diagnosis of a CPanNET was made in half of cases. After a median follow-up of 70 months, the 5- and 10-year overall survival of CPanNETs were 94.6% and 75.4%, respectively, compared to 93.9% and 87% for SPanNETs (p>0.05). The 5- and 10-year DFS rates were 95.1% and 90.8% for CPanNETs, and 84.3%, and 78.7% for SPanNETs, respectively (p>0.05) Conclusion: CPanNETs are rare, non-functional and well differentiated neoplasms. After surgical resection, they share the excellent outcome with well-differentiated SPanNET for both survival and recurrence Keywords: cystic
Surgical Strategies and Selection Criteria for Patients with Liver Metastasis from Neuroendocrine Tumors: Personal Experience

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Introduction: The role of surgical treatment of liver metastasis from neuroendocrine neoplasm (NET) is still a debated issue, and the management of these patients is entrusted to the practical experience of single centers. The main problem is that there are not available randomized trials comparing surgical resection to untreated patients or other liver directed therapy.

Aim(s): To resume the main surgical strategy and selection criteria adopted and compare the results to our experience to achieve a flow chart for a personalized management of these patients.

Materials and methods: Between 2005 and 2015, 284 patients with histologic diagnosis of NET afferent to Ca’ Foncello Hospital in Treviso were collected. In this group, 119 cases of gastro-entero-pancreatic NET (GEP-NET) were identified, 37 of them with liver metastasis.

Results: 9 patients with liver metastasis underwent surgical resection. Statistical analysis demonstrated a better overall survival of resected patients (p=0.035). Furthermore, poor differentiated NET (G3) presented worse prognosis than well differentiated (G1/G2) NET, and the same results were obtained considering Ki67 values alone (p=0.0001).

Conclusion: Data evaluation suggests that surgery has so far the best results in the treatment of NET liver metastasis, especially when associated to ablative procedures. Patients with advanced NET are highly heterogeneous, and can benefit from a wide panel of therapeutic strategy, with different modality based on grading, metastatic pattern and clinical features.

Keywords: net, liver metastasis, surgery
Ki67 Is Able to Predict Pancreatic NENs Prognosis Irrespective of Their Size

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Introduction: In pancreatic neuroendocrine neoplasms (pNENs), size <20mm and Ki67 ≤2% suggest indolent behavior. None of these factors alone predicts prognosis. No other predictive factors have been suggested. Aim(s): We investigated factors predictive of progression in 80 pNEN patients (pts) surgically treated from 1994 to 2014. Materials and methods: 76 pts had Ki67 <20%; 45 had no liver metastasis (Ki67 ≤2%, n=24; Ki67 2-20%, n=21). Results: Median PFS was 51 months (95% CI 31-58). With pts with Ki67 <2% and no metastasis as reference, HR for progression was 3.34 for pts with Ki67 2-20% without metastasis (1.18-9.50), 5.91 (2.42-14.4) for metastatic pts and 28.8 (7.31-113) when Ki67 >20%. No pt with Ki67 <2% and no metastasis had progressed 1 year after surgery. Progression was associated with liver (HR 3.63; 1.98-6.64) and lymph node metastasis (1.90; 1.07-3.36), parenchymal (2.23; 1.11-4.39) and perineural invasion (1.98; 1.11-3.53), and Ki67 >2% (2.67; 1.44-4.97). In non-metastatic pts, only perineural invasion predicted progression. Tumor size (<20 vs ≥20mm) was not a predictive factor at any analysis. Conclusion: Ki67 is the major prognostic factor in pNEN. Ki67 and liver metastasis identify different progression risks. Tumor size is not a predictive factor. Pts with Ki67 <2% and no metastasis may receive delayed surgery. Keywords: ki67, pfs, pancreatic, nen
Introduction: Small pancreatic neuroendocrine tumours (pNETs) present a management dilemma between surveillance and resection. Aim(s): To assess the malignant characteristics of small pNETs in a retrospective, multicentre, operative patient cohort. Materials and methods: Patients were identified from 5 hospitals using inclusion criteria of non-functional, non-familial, resected pNETs of all stages and grades. Logistic and cox regression were performed using SPSSv22. Results: 227 patients with a resected pNET were identified. 66 (29%) had tumours $\leq 2$cm. Malignancy was defined as local, vascular or lymphatic invasion or distant metastasis and was confirmed in 165 (73%) patients; 25 (38%) tumours $\leq 2$cm were malignant, compared to 140 (87%) $>2$cm, $p<0.001$. The smallest primary with nodal metastasis was 6mm and with liver metastasis, 10mm. ROC analysis showed that malignancy was identified with 84% sensitivity using the cut-off of 20mm (AUC 0.823), or 97% using 10mm. The median survival of this cohort was 202 months, and did not significantly differ across the 2cm threshold ($p=0.122$). Importantly, diameter was not predictive of overall survival for all diameters ($p=0.268$), suggesting a shared tumour biology. Conclusion: 1. 38% of pNETs $\leq 2$cm displayed malignant features. 2. Metastatic disease was reported in primaries as small as 6mm; the current surveillance cut-off of 20mm would miss 9% of malignancy. 3. Survival was not significantly better for tumours $\leq 2$cm, reflecting the malignant potential shared by all pNETs Keywords: pnet, surveillance, incidental
Measurement in Blood of a Circulating NET mRNA Gene to Predict Surgical Efficacy

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Introduction: Surgery is the only curative treatment for GEP-NETs, but identifying post-surgery residual disease is difficult and often delayed. **Aim(s):** Examine whether a blood multianalyte neuroendocrine gene transcript assay defines the completeness of surgical resection and identifies residual disease. **Materials and methods:** GEP-NETs (n=48) were evaluated. Group I (retrospective: n=33); Group II (prospective: n=15). Blood samples were obtained before and 1 month after surgery. Disease status was evaluated at 6 months (CT/MRI; 68Ga DOTA- PET/CT, 99mTc TOC SPECT/CT). CgA levels were the comparator. **Results:** Circulating NET transcripts were elevated in 100% pre-operatively whereas CgA was 56% (χ^2=19, p<0.0001). In cohort I, R0 resection reduced NETest from 71±7% (pre-surgery) to 19%±2% at 1 month (p<0.0001) in those (n=18) who subsequently had no image evidence of disease (NED). Values were decreased with cytoreduction but known residual disease (82±5% to 64%±5%, p<0.02). In cohort II, the NED group exhibited significantly lower levels at 1 month (21±6 vs. 68±8%, p<0.02). Ten patients with levels >33% (1 month) originally considered R0, developed image recurrence by 6 months. CgA was non-informative. **Conclusion:** Blood NET transcripts correlate with completeness of surgical resection. Residual disease can be identified within one month of surgery. The alteration of management strategy with early initiation of additional therapy seems plausibly advantageous. **Keywords:** netest, surgery, biomarker, net
Outcome of Surgical Resection after Neoadjuvant Peptide Receptor Radionuclide Therapy (PRRT) for Pancreatic Neuroendocrine Neoplasms: A Case-Matched Analysis

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Introduction: Neoadjuvant Peptide receptor radionuclide therapy (NPRRT) can be an option for advanced pancreatic neuroendocrine neoplasms (PNEN) before surgery. Is not clear if NPRRT increases postoperative morbidity

Aim(s): To evaluate effects of NPRRT in patients with PNEN

Materials and methods: Pts with metastatic and/or locally advanced PNEN who underwent NPRRT were compared with pts who underwent upfront surgery (control group). Pts were matched for tumor size, grading, staging and intent of resection

Results: 20 pts underwent NPRRT+pancreatic resection, 6 pts had liver metastases, 14 presence of organ/vascular infiltration. After NPRRT the median tumor size decreases from 59 to 50 mm (P=0.047). Histology revealed a PNEN-G1 in 10 pts, G2 in 7, G3 in 3. Pre and post-operative tumor grading was concordant in 13 pts,5 were upstaged, 2 were downstaged. NRRT group had lower risk of developing pancreatic fistula (25% vs 65%, P=0.011), overall complications rate was similar (45% vs 60%, P=0.342). The 2 groups had similar distribution of tumor grading, T stage, TNM stage, R2 resection, necrosis, microvascular and perineural invasion. Control group pts had more nodal metastases (80% vs 35%, P=0.004). The 2-year progression free survival rate was 85% for the NPRRT group vs 59% in the control group (P=0.302). Independent predictors of progression free survival were PNEC-G3 and stage IV tumor

Conclusion: Pancreatic resection for PNEN after NPRRT is safe and associated with a lower risk of developing pancreatic fistula

Keywords: neoadjuvant prrt, pnen, surgery
Introduction: The evidence base when to operate MEN1 related non-functioning pancreatic neuroendocrine tumors (NF-pNETs) is meager. **Aim(s):** To assess if surgery for MEN1 related NF-pNETs is effective for improving overall survival and preventing liver metastasis. **Materials and methods:** MEN1 Patients diagnosed with NF-pNETs between 1990-2014 were selected from the DutchMEN1 study group database, including >90% of the Dutch MEN1 population. The effect of surgery was estimated using time-dependent Cox analysis with propensity score restriction and adjustment. **Results:** Of the 152 patients, 53 underwent surgery and 99 were managed by watchful waiting. In the surgery group, tumors were larger and faster-growing, patients were younger, more often male and were more often treated in centers that operated more frequently. Surgery for NF-pNETs was not associated with a significantly lower risk of liver metastases or death, (adjusted Hazard Ratio (HR) = 0.73(0.25-2.11)). Adjusted HR's after stratification by tumor size were: NF-pNETs <2cm = 2.04(0.31-13.59) and NF-pNETs 2-3 cm= 1.38(0.09-20.31). Five out of the six patients with NF-pNETs >3cm managed by watchful waiting developed liver metastases or died compared with six out of the 16 patients who underwent surgery. **Conclusion:** MEN1 patients with NF-pNETs <2cm can be managed by watchful waiting, hereby avoiding major surgery without loss of oncological safety. The decision to operate patients with NF-pNETs between 2 to 3 cm becomes debatable. Surgery for patients with NF-pNETs >3cm seems justifiable. **Keywords:** men1
Minimal Risk of Persistent or Recurrent Hypoglycemia after MEN1-Related Insulinoma Surgery. A Large International Cohort Study

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Introduction: Current literature states that 15-30% of the MEN1 patients suffer from hypoglycemia after insulinoma surgery. Aim(s): To determine the optimal surgical strategy to treat MEN1 related insulinomas. Materials and methods: A total of 96 MEN1 patients with insulinomas underwent surgery between 1990-2015 at one of the 46 participating hospitals from Europe and North America. Post-operative hypoglycemia, complications, and pancreatic insufficiency were captured. Results: Seven percent of the patients had persistent or recurrent hypoglycemia. None of the 9 patients who were operated for a proximal insulinoma developed hypoglycemia. Of the 54 patients with a distal insulinoma, one patient had persistent disease after a distal pancreatectomy (1/41), and one patient developed a new insulinoma after an enucleation (1/13). Of the 33 patients operated for multiple insulinomas, 1/26 patients developed an insulin producing liver metastasis after a distal pancreatectomy combined with surgery of the pancreatic head. Four out of seven patients developed recurrent disease after other surgical approaches for multiple insulinomas. Patients who underwent an enucleation did not develop pancreatic insufficiency. Conclusion: MEN1 related insulinoma surgery is more successful than previously thought. In MEN1 patients with a solitary insulinoma, an enucleation seems reasonable, if surgically feasible. A distal pancreatectomy combined with surgery of the pancreatic head is favorable for MEN1 patients with multiple insulinomas throughout the pancreas. Keywords: men1
Gallbladder Neuroendocrine Carcinoma. Is It Different from Adenocarcinoma?

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\textbf{Introduction:} Literature on Gallbladder neuroendocrine carcinoma is limited. \textbf{Aim(s):} To elucidate the clinicopathological features and outcomes after surgery for Gallbladder neuroendocrine carcinoma and compare it with adenocarcinoma \textbf{Materials and methods:} This was a retrospective analysis of Gallbladder cancer (GBC) patients operated between August 2009 and June 2015. Patients with Gallbladder neuroendocrine carcinoma were compared with adenocarcinoma for clinicopathologic features and surgical outcomes. \textbf{Results:} During the study period, 263 patients of primary GBC underwent curative resection. Of these, 9 had neuroendocrine carcinoma (Group A), whereas 232 had adenocarcinoma (Group B). Abdominal pain was the most common symptom in both groups. However, presentation with vomiting and an abdominal lump was more common in Group A (P = 0.03 and < 0.01, respectively). Group A had a significantly larger tumor size (7.4 vs 4.3 cm, P = 0.01) and a higher incidence of adjacent organ involvement requiring extended resections (77.8% vs 28.9%, P < 0.01). There was no significant difference in the incidence of lymph node metastasis between two groups (88.9% vs 83.2%, P = 1.00). There was no significant difference in the median survival after curative resection between the 2 groups (26 vs 31 months, P = 0.29). \textbf{Conclusion:} The Gallbladder neuroendocrine carcinoma presented at an advanced T stage compared to adenocarcinoma. Despite the higher T stage, curative resection could be achieved with a comparable survival. \textbf{Keywords:} gallbladder neuroendocrine carcinoma
(O23)
FNA Under Percutaneous Ultrasound or Endoscopic Ultrasound for Pre-Operative Diagnosis and Grading Determination in PanNET. Are They Reliable to Define a Tailored Therapy?

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Introduction: Fine-needle aspiration cytology (FNA) under percutaneous ultrasound guided (pUS) or endoscopic ultrasound (EUS) control is a minimally invasive technique allowing diagnosis and grading determination in pancreatic neuroendocrine tumors (PanNET). Obtaining a correct cytological diagnosis is crucial for a tailored therapy. Aim(s): To determine the diagnostic accuracy of cytological samples obtained by EUS-FNA and pUS-FNA in PanNET.

Materials and methods: Data of patients submitted to pancreatic resection for PanNET from 2010 to 2016 at the Authors Institution were retrospectively reviewed. A comparison between pre-operative cytology and final histology was performed.

Results: During the study period, 268 patients underwent pancreatic surgery and in 49 cases (18.3%) a pre-operative FNA was done. EUS-FNA and pUS-FNA were performed respectively in 35 (71.4%) and 14 (28.6%) cases. A diagnostic concordance was observed in 40 cases (81.6%); in 6 cases (12.3%) the cytology was non-diagnostic; 3 cytological examinations (6.1%) were misinterpreted (2 adenocarcinomas and 1 mucinous neoplasm). Ki67% assessment was made on 27 FNA (55.1%). A concordance of grading was found in 21 cases (77.8%); most of the discrepancies were among the G2 diagnosed in cytology (2 G1 and 2 G3 in histology). No differences in reliability between EUS-FNA and pUS-FNA was found.

Conclusion: FNA is a valid instrument for the diagnosis and the determination of grading of PanNET. Our study shows a high concordance rate between pre-operative cytology and final histology.

Keywords: fna, ki67
Introduction: Malignant potential of sporadic nonmetastatic nonfunctional pancreatic neuroendocrine tumors (sNF-PNET) is difficult to preoperatively predict. Aim(s): To assess the prognosis of resected (≤ 2 cm) sNF-PNET.

Materials and methods: Patients with resected sNF-PNET were identified from databases of 16 European surgical centers. Postoperative outcomes as well as, risk factors for recurrence were identified by uni- and multivariate analyses. Results: sNF-PNET was resected in 210 patients and about 65% (n=138) were asymptomatic. Median age was 60 years, median tumor size was 15mm (radiologically underestimated in about 10% of patients), parenchyma-sparing surgery was performed in 42% of tumors. Postoperative mortality was 0.5% (n=1) and severe morbidity rate was 14.3% (n=30), 10.2% of patients (n=14) had metastatic lymph nodes. The 1, 3 and 5-year disease-free survival rates were 96.4%, 93.5%, and 93.5%, respectively. Of preoperatively accessible factors, tumor size and presence of biliary or pancreatic duct dilatation on preoperative CT-scan were independently associated with recurrence. All patients with tumors sized ≤10mm were disease free at last follow up. The 1, 3 and 5-year disease-free survival rates for patients with tumors sized 11-20 mm on preoperative imaging were 95.1%, 91%, and 87.3% respectively. Conclusion: In sNF-PNETs, the presence of biliary or pancreatic duct dilatation on preoperative CT-scan advocate for surgical treatment. In the remaining patients, a wait-and-see policy might be considered. Keywords: pancreatic nets
Meta-Analysis of Liver Resection versus Nonsurgical Treatments for Pancreatic Neuroendocrine Tumors with Liver Metastases

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Introduction: Available data comparing the efficacy of different treatment regimens are rarely found. No meta-analyses have compared liver resection with other nonsurgical treatments in resectable liver metastases from pNETs. Aim(s): Studies have reported limited evidence of the benefits and harms of various regimens for the treatment of pNETs with liver metastases. This meta-analysis aimed to evaluate the efficacy of liver resection versus nonsurgical treatments in patients with pNET. Materials and methods: A meta-analysis was performed to investigate the differences in the efficacy of liver resection and nonsurgical treatments based on the evaluation of 30-day mortality, symptom relief rate, median survival time, and 2-, 3-, or 5-year survival using a random-effects model. Results: A total of seven studies were included in the analysis. The results demonstrated that liver resection was significantly associated with a higher rate of symptom relief, longer median survival time, higher 2- or 3-year survival rates, as well as a higher 5-year survival rate. There was no significant difference in 30-day mortality among patients with pNETs who were treated by liver resection and nonsurgical therapy or survival between functional and nonfunctional pNETs. Conclusion: Liver resection has a favorable prognostic outcome in terms of higher postoperative symptom relief rates and longer survival rates. Keywords: meta-analysis, pancreatic neuroendocrine tumors (p-nets), liver metastasis, liver resection
Introduction: Somatostatin receptors (SSTRs) play a key role in the regulation of cell proliferation and have been identified in a proportion of aggressive poorly differentiated neuroendocrine neoplasms, including small cell lung carcinomas (SCLCs). Aim(s): This study aimed to assess the prognostic value of SSTR subtype 2A (SSTR2A) expression in SCLC patients with limited- and extensive-disease. Materials and methods: SSTR2A expression was evaluated by immunohistochemistry (IHC) with the monoclonal antibody UMB-1 in 52 biopsy samples from primary tumors (n=45) or metastases (n=7) of SCLC patients. SSTR2A expression status in tumor was correlated to progression-free (PFS) and overall survival (OS). Results: Positive SSTR2A immunostaining was seen on the cell surface in 19 (36.5%) of 52 examined SCLCs. The SSTR2A score was 2 in 12 (23.1%), and -3 in 7 (13.5%) tumors. The remaining 33 (63.5%) SCLCs showed low or absent expression levels (score 0/1). Median progression free survival after platinum based chemotherapy was 5.74 months (95% CI 3.5-8) for SSTR2A-score 2/3 and 5.77 months (95% CI 2.6-9) for SSTR2A-score 0/1 (p=0.8). Median overall survival was not reached in patients with high expression levels and was 27.2 months in patients with low SSTR2A expression levels (p=0.8). Conclusion: Preliminary data suggests that, although SSTR2A was shown to be expressed by IHC in up to 37% of tumors, SSTR2A-expression status do not correlated with time to progression and overall survival in SCLC patients. Keywords: small cell carcinoma, lung, immunohistochemistry
Primary Neuroendocrine Carcinoma of the Breast: A Diagnostic Approach to the Special Type of Breast Malignancy

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Introduction: WHO classification from 2003 defines primary neuroendocrine carcinomas (NEC) of the breast as a group of tumors with expression of neuroendocrine markers in more than 50% of tumor cells. In the current WHO classification this category is renamed to “carcinomas with neuroendocrine features” without defined clear-cut of the percentage of tumor cells positive for neuroendocrine markers. Aim(s): To evaluate diagnostic criteria for primary breast NEC. Materials and methods: Histopathologic reports of patients with breast carcinoma in the last 10 years were analyzed; cases of breast NEC were selected and reviewed for the positivity for neuroendocrine markers, estrogen receptors (ER), progesterone receptors (PR), HER-2/neu and presence of in situ component. Results: Among 11034 cases of breast carcinoma, 37 primary NEC (incidence rate: 0.3%), and 3 metastatic NEC were identified. Synaptophysin was diffusely positive in 35 (94.6%), chromogranin-A in 32 (86.5%) and NSE in 21 (56.6%). 34 (91.9%) were ER+; 32 (86.5%) PR+; 3 cases (8.1%) were triple-negative and only one case was HER-2/neu positive. Five out of seven reported cases had ductal carcinoma in situ (CIS) component. Conclusion: Breast NEC is a rare tumor. Positivity for synaptophysin and chromogranin-A is evident in the majority of primary breast NEC. Metastasis must be ruled out to declare it primary. Helpful characteristics for accurate diagnosis are presence of CIS, ER and PR positivity. Keywords: breast cancer, special types, carcinoma with neuroendocrine features, neuroendocrine markers
Introduction: Bronchopulmonary NETs (BPNETs) exhibit indolent to aggressive behavior. Imaging, histology and biochemistry are limited in accurately defining malignancy or progression. A blood based NET multigene test is effective in diagnosing GEP-NET progression and therapy response. Aim(s): Assess the efficacy of NETest in BPNET diagnosis and identification of progressive disease. Materials and methods: Material: BPNETs: (n=108), controls (n=90), COPD (n=18) and lung cancers (n=12). Measurements: NETest (+ve >14%) by qPCR; CgA by ELISA (normal <109ng/ml); disease status by imaging. Carcinoids were typical TC: n=64, atypical AC: n=44. Clinico-histological groups were AC/SD or AC/PD; TC/SD or TC/PD by RECIST. Progressive disease (PD): 43% AC and 23% TC. Analysis: 2-tailed Mann-Whitney U-tests and ROC-statistics. Results: NETest: 100% in all BPNETs (levels 49±3%) vs controls (6±1%, p<0.0001). COPD (24±0.5%) and cancers were 15±2%. AUC for differentiating controls was 0.94±0.03 (p<0.0001) and lung diseases (AUC: 0.90±0.02, p<0.0001). NETest did not differentiate TC (46±3%) from AC (55±4%). NETest accurately identified PD (74±4%) vs SD (38±3%, p<0.001, AUC: 0.85). Metrics measuring for clinical behavior of TC/AC were >85%. CgA was non-informative. Conclusion: The blood-based NETest identified BPNETs (100%) and accurately differentiated controls/lung disease (>95%). Progressive disease was accurately defined irrespective of histological subtype. Transcript analysis indicates that histological identification of TC/AC may require reconsideration. Keywords: net
Renal Neuroendocrine Tumors (rNETs): A Single-Center Experience

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Introduction: rNETs are rare tumors and little is known about their natural history. Aim(s): To describe presenting features and outcomes in rNETs pts seen at Mayo Clinic 2000–2015. Materials and methods: Pts in the Mayo Clinic Cancer Registry were identified. Survival was calculated with the Kaplan-Meier method. Results: 14 rNETs pts were included. Median age at diagnosis (dx) was 48.5 years. 9 were females, 8 pts had pain at dx, 2 each had flushing and hematuria. 4 pts had a horseshoe kidney. WHO grade was G1:36%, G2:43% and G3:7%. T stage was T1:29%, T2:29% and T3:36%. 8 pts had nodal and 4 had distant metastases at dx. Bone metastases were common (2 at dx, 4 later). Radical or partial nephrectomy was performed in 13 pts. Nodal and/or metastatic resection/ablation was done in 9 pts. Ten pts had R0 resection. Nine pts had recurrence (median TTR 15.5 months) and 8 had systemic therapy at recurrence. 7 pts had a somatostatin analog, 4 had cytotoxic chemotherapy and 1 had everolimus. 2 pts had a radiographic response, 4 had stable disease and 5 progressed. Six pts received second-line therapy with no objective responses. At a mean follow of 50 months, 4 pts were free of disease, 5 had stable disease and 3 had progressed. Two pts had died, one from renal NET. The median overall survival from dx was 99.9 months. Conclusion: rNETs are rare tumors. Most patients had a complete resection but recurrences were common. Despite frequent recurrences, overall survival is long. The role of systemic therapy is uncertain. Keywords: renal, kidney, net, carcinoid
Lung Carcinoid: Role of NSE and Imaging Techniques in Long-Term Follow-Up of Malignancy Recurrence

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Introduction: Typical and atypical Lung Carcinoids (LC) are rare neuroendocrine tumors usually characterized by good prognosis. Malignancy recurrence (MR) is uncommon but may occur even after several years; a close long-term follow-up is required. Aim(s): Since no commonly accepted clinical guidelines on long-term follow-up are available so far, the aim of this study is to evaluate the post-surgical follow-up and the progression-free survival (PFS) of LC, in order to better elucidate the indication for imaging and/or biochemical marker (BM) screening. Materials and methods: Clinical data of 37 patients diagnosed with LC from 1986 to 2015 were collected and compared through a database. We focused our attention on Neuron Specific Enolase (NSE) assessment and on imaging techniques (chest X-Ray and chest-CT). Results: 7 patients showed MR with differently located metastases (local, mediastinal lymph nodes, liver and bone); 2 of these patients showed slightly increased NSE levels after many years from MR. PFSs ranged from <1 year up to 15,5 years. Post-surgical MR had a bimodal distribution: one peak within the first 5 years and the other after 8-9 years. Chest X-Ray screening was unable to identify local MR, that was detected by chest-CT. Conclusion: On the basis of our results, NSE values cannot be considered as a reliable BM for MR in LC. Moreover, since chest-CT has proved higher diagnostic sensitivity, it should be recommended as annual screening during the two time frames at higher risk of MR. Keywords: lung carcinoid, follow-up, nse, imaging
Introduction: Nausea and vomiting are common complaints during pregnancy. However, primary hyperparathyroidism in pregnancy can mimic these gastrointestinal symptoms and challenge the physician. Aim(s): We report the case of a 33-year-old woman that was diagnosed with primary hyperparathyroidism after developing severe vomiting and nausea. Materials and methods: N.A. Results: After the initial management at the emergency department, the further evaluation found severe hypercalcemia with an elevated parathyroid hormone level and right parathyroid adenoma. Conclusion: The primary hyperparathyroidism in pregnancy is associated with significant maternal and fetal morbidity and mortality. We review through this case the diagnostic and therapeutic challenges associated with primary hyperparathyroidism in pregnancy. Keywords: primary hyperparathyroidism, adenoma, pregnancy
Un Unusual Tumor Association in Acromegaly

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Introduction: Acromegaly is associated with an increased risk for malignancies. Only a case of pseudomyxoma peritonei with ovarian and appendicular sequential tumors in acromegaly was described. Aim(s): We report the case of appendicular adenocarcinoma in acromegaly in progression despite controlled disease. Materials and methods: A 59 years old woman underwent partial neurosurgery in 2006 for invasive GHoma. Pt started treatment with somatostatin analogues and she underwent second neurosurgery in 2008. In 2010 for resistant disease pt was enrolled in PAOLA study with normalization of GH secretion. In January 2015 a left ovarian cyst was found and pt was followed-up with gynecological ultrasound. In September 2016 for increase in size and appearance of a contralateral lesion pt was oophorectomized-hysterectomized. Histological examination showed infiltration of mucinous adenocarcinoma of probably gastrointestinal origin with a neuroendocrine cell line differentiation. Colonoscopy and gastroscopy were negative. Ecoendoscopy-guided biopsy of gastric wall revealed metastasis of mucinous adenocarcinoma. Results: In 2011 patient had undergone appendectomy for acute appendicitis. The revision of the histological material revealed the presence of appendicular adenocarcinoma. So pt had developed a metastatic disease from a misunderstood appendicular neoplasm. Conclusion: The described association is unusual and reinforced the well-known importance of oncological screening in acromegalic patients for early diagnosis of cancer. Keywords: acromegaly, appendicular tumor
Detection of Metastatic Insulinoma with 68Ga-NODAGA-Exendin-4 PET/CT in a Young Child – A Case Report

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Introduction: Malignant insulinomas are extremely rare in children. Localizing metastases of insulinoma is challenging. Imaging modalities like CT and MRI show limited results. Somatostatin-receptor (SSTR) imaging (SRS) performs better. However, a subgroup of malignant insulinoma lack SSRT-2 and can, therefore, not be localized using SRS. We propose that in these cases GLP-1R imaging, using the stable GLP-1 analog exendin, could play an important role. Aim(s): We here report a rare case of an 11-year old boy with malignant insulinoma, which shows the diagnostic relevance of GLP-1R PET/CT.

Materials and methods: An 11-year old boy presented with recurrent hypoglycemia after pancreatectomy. Metastases of the insulinoma were suspected. MRI and CT showed multiple lesions diffuse in the liver, suggestive of steatosis. The presence of insulinoma metastases could not be confirmed. 68Ga-DOTATATE PET/CT did not show pathological accumulation in the liver. We performed a 68Ga-NODAGA-exendin-4 PET/CT 4 years after the initial operation. Results: 68Ga-NODAGA-exendin-4 PET images showed inhomogeneous uptake in the liver with clear hotspots corresponding to the abnormalities identified on CT, pointing to multiple liver metastases. Conclusion: This result indicates the important contribution of GLP1-R imaging in localization of insulinoma in the liver, where other imaging modalities do not allow the differentiation between metastases and peritumoral steatosis which is often present in these cases. Keywords: metastatic insulinoma, glp-1r, pet, exendin
(Q4)
Pure Alpha-Fetoprotein-Producing Pancreatic Neuroendocrine Tumors: A Case Report

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Introduction: Pancreatic neuroendocrine neoplasms (pNENs) with alpha-fetoprotein (AFP)-producing are extremely rare, and only one case was reported as pure AFP-producing pancreatic neuroendocrine carcinoma (pNEC) until today. Aim(s): The present study reports the first case of pure AFP-producing pancreatic neuroendocrine tumor (pNET) (G2).

Materials and methods: A 62-year-old male patient was accepted palliative resection of the pancreatic body, tail and the most of liver metastases because of serum AFP levels was elevatory and both of pancreatic and liver mass which were enlarged by 3 cycles of long-acting-release octreotide (Sandostain LAR). Histopathologic examination determined the diagnosis of an AFP-producing pNET. The tumor was positive for chromogranin A, synaptophysin, Cluster of Differentiation 56 and AFP. The mitotic count was about 1 per 10 high-power fields and the Ki-67 index was about 10%. Results: The patient received more lines therapy such as Sandostain LAR, Hepatic artery embolization, Sunitinib, Capecitabine plus Temozolomide, Everolimus and so on after operation. The serum AFP was be detected regularly and its change was related to the treatment effect. The serum AFP decreased to 28 ng/ml after operation while increased to the maximum value at 3131 ng/ml during tumor progression.

Conclusion: This was the first case to be reported as pure AFP-producing pNET (G2). Serum AFP levels may be clinically important in pNENs which provide positive information for the change of tumors. Keywords: alpha-fetoprotein, pancreatic neuroendocrine tumors
Large Cell Metastatic Pancreatic Neuroendocrine Carcinoma Treated with Somatostatin Analogues


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Introduction: Poorly differentiated neuroendocrine carcinoma of the pancreas are rare malignant tumors with a poor prognosis. Aim(s): Materials and methods: Results: We report a case of a 55 year-old-male with large cell metastatic pancreatic neuroendocrine carcinoma treated for 14 months with octreotide LAR (long acting release) having stable disease(SD) and not responding to chemotherapy. The somatostatin analogues introduced after un episode of diarrhea controlled the disease. Progression-free survival as determined by 3-monthly CT scans, was obtained for 14 months, with the need to increase octreotide LAR dose. After more than a year, the patient deteriorated along with progressive disease. The cisplatinum-etoposide regimen was re-challenged, but after 3 cycles, a rapid clinical decline was noted. Conclusion: This unexpected event in the course of the disease (diarrhea) could be the beginning of carcinoid syndrome and the octreotide LAR helped the episode of diarrhea to pass, but also had a good control over the disease itself. Keywords: carcinoid syndrome, somatostatin analogues
Small Cell Metastatic Ascending Colon Neuroendocrine Carcinoma

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Introduction: Poorly differentiated neuroendocrine carcinoma (NEC) of the gastrointestinal tract are rare malignant tumors with a poor prognosis. Aim(s): Materials and methods: Results: We present the case of a 63 year-old-women with a poorly differentiated NEC of the ascending colon with liver, peritoneal and abdominal lymph nodes metastases followed in our clinic for 46 months and alive. A right hemicolecctomy was performed. Histologically was diagnosed a small-cell carcinoma and immunohistochemical staining for synaptophysin was diffuse positive, chromogranin A rarely positive, NSE positive in tumor cells and Ki67 index 60%. The patient received cisplatin+etoposide with partial response after 3 months of therapy but with renal insufficiency and gr 2 diarrheea. The patient received somatostatin analogue (SSA) and after 11 months, CT scan showed progressive disease. This brought the need to add CAPOX regimen. The patient had severe hypersensitivity reaction to oxaliplatin and continued to receive capecitabine. After 13 months of capecitabine and lanreotide autogel, at CT scan was registered complete response. After 46 months from the diagnosis the patient continues capecitabine and lanreotide autogel. Conclusion: Having a multiple site metastasized poorly differentiated neuroendocrine colonic carcinoma, with the resection of the primary tumor, with unexpected good response to chemotherapy, may be the result of chromogranin level in tumoral cells which could pay a role as a predictive factor for chemotherapy response. Keywords: chemotherapy, metastases
Sinonasal Neuroendocrine Small Blue Cell Tumour (SNBCT) Presenting with Bone Marrow Failure – A Very Rare Diagnostic and Therapeutic Challenge

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Introduction: A 75 year old female presented with rapid onset right neck swelling and nasal bleeding. CT showed an infiltrative soft tissue mass involving the entire right nasal cavity and a lymph node mass in the right neck. Aim(s): Materials and methods: Results: Nasal biopsy showed a small blue cell tumour with relatively monomorphic cells with areas of necrosis; IHC showed diffuse, strong positivity for CD56 and NSE but negative for other neuroendocrine markers (synaptophysin and chromogranin A). Subsequently, the patient presented with widespread non-traumatic bruising. Blood tests showed bone marrow failure with Hb 74 and platelets 17. Bone marrow trephine confirmed metastatic disease. The patient consented to and was commenced on low dose palliative doxorubicin/cyclophosphamide chemotherapy, supported with alternate day platelet transfusions. Despite initial clinical response in neck nodes and decreased nasal bleeding, sadly she was admitted after 2 weeks with confusion due to a massive subdural haemorrhage, and died 2 days later. Conclusion: Sinonasal neuroendocrine small blue cell tumour (esthesioneuroblastoma) is a rare primary malignancy of the nasal sinuses. Although metastatic bone disease can occur, we have found no reported case in the literature of SNBCT presenting with complete bone marrow replacement. We believe combination chemotherapy was a valid treatment option in addition to supportive care in this case. Keywords: sinonasal, neuroendocrine, small, blue, cell, tumors, esthesioneuroblastoma, diagnosis, treatment, bone, marrow, metastases
A Case with Multiple Neuroendocrine Tumors

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\textbf{Introduction:} Multiple endocrine neoplasia (MEN) is characterized by the occurrence of tumours involving two or more endocrine glands. MEN 1 is characterized by parathyroid adenoma, pancreaticoduodenal neuroendocrine tumors (PNTs), and pituitary adenomas. \textbf{Aim(s):} We report the case of a 28-year-old woman hospitalized for weight loss and diarrhea. \textbf{Materials and methods:} A CT scan was performed and showed 2 small lesions in the pancreas, a mass in the left lung and multiple cystic tumours in the liver. The patient underwent endoscopic ultrasound with biopsies of the pancreatic lesions which showed well differentiated neuroendocrine tumour. An Octreo PET was positive for the pancreas tumours and for liver lesions. PET CT scan was only positive for the lung mass and the liver metastases. High level of Chromogranin A was found (518 mcg/l) as well as Urinary 5HIAA (90mg/24h). Transthoracic biopsy of the lung mass demonstrated a well differentiated neuroendocrine tumor. We started subcutaneous somatostatin analogs which improved the diarrhea. A CT scan performed after 2 months showed partial response. The patient also had parathyroid adenoma with primary hyperparathyroidism. Hypophysis imaging was negative. \textbf{Results:} The association of two neuroendocrine tumors, and parathyroid adenoma led us to suspect the patient to have a type 1 MEN. \textbf{Conclusion:} The majority of tumors in people with MEN1 are benign. We report a case with suspicion of MEN 1 with cystic metastases in the liver and carcinoid syndrome, a rare entity. \textbf{Keywords:} neuroendocrine tumor, men
Hypoglycemias Appearing in a Patient Suffering from Poorly Differentiated Neuroendocrine Tumor for Three Years

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Introduction: Insulinomas are the most common functional PNENs and they have a weak malignant potential (<10%) Aim(s): A 51-year-old woman was hospitalized for unconsciousness on hypoglycemia at home. This patient is known and currently treated for a poorly differentiated pancreatic neuroendocrine tumor (Ki67 = 40%) with lymph nodes and liver metastases since March 2013. Materials and methods: The neoplasm has begun in 2013, with an unknown primary lesion, inter-aorticocaves lymph nodes and liver metastases. The primary tumor appeared in the pancreas head one year later when disease progressed after multiple therapies including chemotherapy, radioembolization and radiation therapy, leading to complete remission for 2 years. Results: The glycemia at home was dosed at 28 mg/dl before refeed. A dosage of insulin at 288,5 pmol/l and C-peptide at 1,42 nmol/l when glycemia was dosed at 31 mg/dl confirmed the diagnosis of an insulinoma. An endoscopic ultrasound-guided biopsy has been performed, but any lesion was visualised neither in the duodenum nor into the pancreas except the nodule described previously. This last was biopsied but it was non contributive. Conclusion: We think that we are in front of a patient with two different pancreatic lesions: the grade III neuroendocrine tumor and the new but invisible insulinoma. This diagnosis is based upon the observation that insulinomas are rarely metastatic. Furthermore, poorly differentiated tumors never evolve towards a well differentiated neoplasm. Keywords: neuroendocrine neoplasm, insulinoma, hypoglycemia
Presentation of a Neuroendocrine Tumor of Breast in a Pakistani Nulliparous Woman

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Introduction: Neuroendocrine tumors of breast are rare and mostly malignant. Aim(s): We are reporting a clinical case of women presented to us with a primary neuroendocrine tumor of breast. Materials and methods: A 48 year unmarried women presented to Sir Ganga Ram Hospital with painless lump in her right breast for last 8 months. She underwent hysterectomy 6 years ago. Examination of lump was done which was 3×3cm in upper outer quadrant of (R) breast. The lump was non adherent to skin or underlying tissue. There was no change in skin, nipple retraction or discharge associated with the lump. No palpable lymph nodes. Systemic examination was done. USG, Mammography, FNAC was advised. ER PR and HER 2 neu was also advised and excision biopsy was done. Results: USG breast showed nodule. Mammography showed a hypodense, opaque, mass lesion. FNAC exhibited atypical cells. Excisional biopsy was performed which exhibited nest cells and cribriform pattern of Neuroendocrine tumor. ER PR status was positive while HER 2 neu was negative. Immuohistochemical analysis was positive for synaptophysin and chromogranin A. USG abdomen, CT abdomen, Chest X-ray were done to rule out any other primary NET. (R) MRM and level 2 axilllary clearance was done. Patient was referred to oncologist for adjuvant chemo. Conclusion: Surgery is the mainstay treatment depending on the staging. However, hormonal therapy should be given. Somatostatin and Interferon are valuable tools in diagnosis and therapy of Breast Nets. The tole of MIBG is still under observation. Keywords: breast
A Long-Term Complete Response (CR) of Avelumab in Patient (pt) with Advanced Merkel Cell Carcinoma (MCC)

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Introduction: MCC is a rare and aggressive cutaneous neuroendocrine cancer linked to exposure to the Merkel Polyomavirus (MCPyV). Cisplatin and VP16 chemo may be an effective treatment for metastatic MCC, but responses are often transient. The blockade of programmed death 1 (PD-1) immune inhibitory pathway by avelumab, an anti-PD-L1 checkpoint inhibitor, is being investigated in solid neoplasms. This strategy can also be of interest in MCC because these tumors often express PD-L1.

Aim(s): to describe a case of advanced MCC in long term CR during immunotherapy with Avelumab

Materials and methods: A 60-year-old man was referred to our center in July 2015 for advanced MCC with nodes and skin lesions, after platinum-based chemo. A phase II, open-label, multicenter trial to investigate the activity and safety of avelumab in pts with advanced MCC was open for enrolment at our institution. The pt was eligible for treatment and started the treatment in August 2015.

Results: The pt received avelumab 10mg/kg IV every 2 weeks. The first CT scan after 6 weeks of treatment showed a 2-fold increase of the size of the lesion, judged as a pseudoprogression. The pt continued avelumab beyond pseudoprogession and on the contrary, the CT scan assessed after 12 weeks showed CR.

Conclusion: PD-L1 blocking antibodies could be promising therapies in pts with advanced MCC. From 16 months to the enrollment of the trial, pt continues avelumab and he shows a good performance status and a long-term CR from one year.

Keywords: merkel cell carcinoma, avelumab
Multivisceral Transplantation and Vascularised Sentinel Forearm Flap for a Metastatic Small Bowel Neuroendocrine Tumour: Update on Follow-Up

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**Introduction:** We previously reported the first documented case of a novel approach in a patient with extensive mesenteric metastases from a small bowel neuroendocrine tumour (SBNET): this combined multivisceral transplantation (MVT) and a vascularised sentinel forearm flap (VSFF) from the same donor. **Aim(s):** We re-present this case after 40-month follow-up post-MVT/VSFF. **Materials and methods:** A 44-year old male patient was diagnosed with a well-differentiated neuroendocrine tumour (G1, Ki67 <1%). Initial gut hormones were elevated: chromogranin A 395pmol/L (normal 0-60), chromogranin B 349 pmol/L (normal 0-150) and 24-hour urine 5-HIAA 643 µmol/L (normal 0-40). Pre-operative 68-Ga DOTATATE PET/CT revealed uptake in an aorto-caval lymph node and bulky mesenteric disease, which was confirmed at laparotomy as stage IV disease encasing the mesenteric root. Numerous lymph nodes and multifocal primary tumour (7 sub-centimetre lesions) were also found at surgery. **Results:** Neoadjuvant 177-Lu PRRT (4 cycles) were followed by modified MVT (stomach, pancreas, spleen, small bowel, right hemi-colon), VSFF and resection of the aorto-caval lymph node. Disease stage was pT3 N1 M0 L1 V0 R0. **Conclusion:** 40 months post-MVT/VSFF the patient is well and fully physically active with no evidence of disease recurrence on follow-up biochemistry or imaging. There was never any rejection in the visceral graft, with one mild, easily treated reaction in the VSFF. (Work published). **Keywords:** small bowel neuroendocrine tumour, multivisceral transplantation, forearm flap, follow-up

Neuroendocrinology 2017;105(suppl 1): 1-338
**Prostate-Specific Membrane Antigen (PSMA) Uptake in a Pancreatic Neuroendocrine Tumor (pNET) Bearing Patient**

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**Introduction:** Prostate-specific membrane antigen (PSMA) is a transmembrane protein overexpressed on both prostate epithelial malignant cells and endothelial cells of tumor-associated neovasculature of many solid cancers. PSMA has been investigated already as a target in staging and detection of prostate cancer. Aim(s): Case Report Materials and methods: A 65-year old male with multiple endocrine neoplasia syndrome (MEN-1) and an history of radically resected prostatic adenocarcinoma. Baseline 68Ga-PET/CT scan documented elevated receptor expression in the head of pancreas and multiple hepatic lesions. FNAB of liver lesion was diagnostic for pancreatic neuroendocrine tumor pNET (Ki67 5%). At diagnosis the patient began SSA treatment which was associated 2 years later with Everolimus due to hepatic progression. For a mild raise in PSA the patient underwent 67Ga-PSMA PET/CT scan which demonstrated a PSMA avid uptake in known neuroendocrine lesions (SUV max 96) Results: Images demonstrated PSMA avid uptake of tracer in pancreatic head and in most of the known liver lesions. To our knowledge this is the second case report about Ga-PSMA PET/CT in assessment of metastatic pNET Conclusion: This case illustrates that PSMA tracer could be useful in detection neoplastic lesions in pNET. Further studies are needed to assess the diagnostic efficacy and role of this functional nuclear imaging as completion of conventional methods for such neoplasms. Keywords: psma, ga psma pet/ct scan, pnet
(Q14)

New MEN1 Gene Mutation Implicated in Familial MEN1 Syndrome Onset

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Introduction: Multiple endocrine neoplasia type 1 (MEN1) is a rare genetic syndrome associated with an increased risk of developing parathyroid, pituitary and pancreatic neuroendocrine tumors. MEN1 has an autosomal dominant pattern of hereditability and it is usually related to mutations in menin coding gene. Aim(s): Case report Materials and methods: A 23-year-old female patient underwent central pancreatectomy for pancreatic neuroendocrine tumor G2 according to WHO 2010. The patient underwent screening for MEN1 syndrome. Results: Analysis of the whole MEN1 gene coding region led to detection of a heterozygous mutation in exon 3, codon 188, P188L, rs199706698. According to literature (ClinVar database) this mutation has an uncertain clinical significance. The 1st grade family members underwent genetic screening: the father carried the same heterozygous mutation together with a new variant of MEN1 gene (exon 2 S38F). He had high serum calcium and PTH values, radiological evidence of hyperplastic parathyroids and avid uptake at scintigraphic evaluation. He underwent to surgical excision with histological diagnosis of parathyroid adenoma and complete resolution of primary hyperparathyroidism. Conclusion: Our observation gives to this previously uncertain mutation a possible pathogenetic role in developing MEN1 syndrome. Keywords: men1 syndrome, men1 gene mutation, neuroendocrine tumor.
Incidentally Detected Pancreatic Neuroendocrine Microadenoma with Lymph Node Metastasis

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Introduction: Pancreatic neuroendocrine microadenomas are tumors with <0.5 cm size and considered as benign. Aim(s): We report on incidentally detected pancreatic neuroendocrine microadenoma with lymph node metastasis.

Materials and methods: - Results: A 78-year-old male was referred to our hospital for surgical resection of distal bile duct carcinoma after initial diagnosis from other institution. Preoperative abdominal CT and MR cholangiography demonstrated abrupt narrowing of distal common bile duct without definite mass or nodule in the pancreas or duodenum. The patient had pylorus-preserving pancreateicoduodenectomy for distal bile duct carcinoma. In distal common bile duct, a 2.1-cm-sized moderately differentiated adenocarcinoma with confinement within bile duct without lymph node metastasis was observed. In addition, a 0.4-cm-sized nodule was noted in the pancreatic head with one peripancreatic lymph node metastasis. Microscopically, the pancreatic nodule consisted of monomorphic tumor cell nests with fine chromatin pattern in fibrotic stroma. The tumor cells are diffusely positive for synaptophysin, chromogranin, and insulin, but negative for glucagon, serotonin, and somatostatin. Ki-67 labeling index was 1.1%. No other focus of neuroendocrine tumor is noted in the remaining pancreas and duodenum. The final diagnosis of pancreatic nodule was pancreatic neuroendocrine microadenoma with lymph node metastasis. Conclusion: This is the rare case of pancreatic neuroendocrine microadenoma with lymph node metastasis. Keywords: neuroendocrine microadenoma
Introduction: Paragangliomas are rare tumors that arise from the sympathetic and parasympathetic ganglia that can possess an inherited trait. Aim(s): We present the case of a 40 year old male with a family history of cervical tumor of unknown histology (father) and high blood pressure (brother-mid 30s).

Materials and methods: The patient’s medical history revealed a large para-aortic retroperitoneal tumor, incidentally detected at age 30, that was excised. The histopathological result was paraganglioma with no follow-up ever since. In 2016, the patient presented to our department complaining of high blood pressure for the past 3 years. Results: High levels of plasma free Normetanephrine (4732 pg/ml) and Chromogranin A (990 ug/L) were detected. The computed tomography showed a tumor of the urinary bladder (7,1/2,9cm) with invasion of the prostate and seminal vesicles, and right hydroureteronephrosis stage I. Due to extensive loco-regional invasion of the tumor, he underwent complete resection of the urinary bladder with local lymph node excision. The histopathological and immunohistochemical examination revealed a multicentric paraganglioma, positive for Cromogranin A and Synaptophisin, with sparse positivity for SSTR2, negative SSTR5 and Ki67 of 20%. The SDHB splicing mutation was found at genetic testing.

Conclusion: The annual evaluation of patients diagnosed with paragangliomas is of the utmost importance. Early detection and treatment of recurrences can save patients and improve their quality of life. Keywords: paragangliomas, sdhb mutation
Unusual Presentation of Carcinoid Syndrome in Chronic Pancreatitis

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Introduction: A carcinoid tumor often causes no symptoms in its early stages and is usually found unexpectedly. The carcinoid syndrome appears when the tumor spreads to the liver. Aim(s): To present a rare case of carcinoid syndrome in a patient with chronic pancreatitis. Materials and methods: In 1982 the patient was diagnosed with chronic pancreatitis. Three years later she underwent a duodenum preserving pancreas head resection followed by pancreatic enzyme supplementation. In 1996 the patient was admitted with abdominal pain and diarrhea with steatorrhea since five years. A CT scan and FDG-PET scan were negative. In 2010 the CT scan was positive for a 1 cm hepatic lesion. FDG-PET was negative. In May 2011 the patient complained watery diarrhea and flushing and in July an abdominal CT scan detected multiple hepatic lesions. Results: Biopsy confirmed a NET secondary. Urinary 5HIIA was 190umol/24h and plasmatic 5HT was 2.20umol/L. Small bowel Rx study detected a lesion in the last ileal loop and octreoscan showed multiple hepatic areas of tracer uptake and a paraumbilical lesion. Ipstyl 120 mg per month. The patient underwent multiple ileal resection and right colectomy. Pathology showed ileal NET (T4N1M1, G2). A liver embolization of the right lobe was performed. The disease was stable 18 months after surgery, then progressed and the patient died 36 months after surgery. Conclusion: Diarrhea is frequent in chronic pancreatitis and may hide carcinoid symptoms until hepatic metastases become massive. Keywords: chronic pancreatitis, carcinoid, diarrhea
SSA-, H1, H2- and Leukotriene Receptor Blockade Eliminates Handicapping Symptoms from Atypical Carcinoid Syndrome

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Introduction: The patient is a female, 59 yrs, previously healthy except from mild allergic rinitis since 12 years of age and at 49 a suspected anaphylaxis after hazelnut intake. Aim(s): In 2011 abdominal pain. CT showed a mediastinal mass, two small liver metastases and a small bowel tumor. She was operated with small bowel, lymph node and liver resection. PAD showed a GI-NET G1 with KI 67 < 2%. Postoperative DOTATOC-PET showed some remaining mediastinal and paraaortal lymph node metastases. Materials and methods: Postoperatively she gradually develops dyspnea, muscle weakness and left abdominal pain. Tumor markers were normal including Chromogranin A+B and CTscan shows stable disease. Results: In 2013 monthly somatostatin analog injections were started and the symptoms decreased. However, mild intermittent shortness of breath remained, as did muscle and joint pain and corneal and skin irritation, raising suspicion of release of mastcellmediators causing an atypical carcinoid syndrome including asthma. Histamine blockade with H1 and H2-blockers was added and the patient improves. When the leukotrien receptor antagonist (montelukast) was further added in 2015, finally all symptoms (pain from spleen region, shortness of breath) disappeared. Conclusion: Her tumor markers are still normal, (Chromogranin A and dU-5-HIAA) but the lymph node metastases persist and some small liver mets are found. Urine analysis by UPLC/MS-MS found high levels of leukotirene E4 and prostaglandin D2 metabolites supporting mast cell activation. Keywords: pgd2
Introduction: Rectal neuroendocrine tumours (NET) constitute 25% of all the digestive NET. Predictive factors of distant metastasis are: size greater than 1cm, high proliferative index and muscularis or lymphovascular invasion. In the absence of these criteria, some authors advocate there is no need for long-term follow-up. Aim(s): Highlight the malignant potential of low grade NETs and importance of follow-up. Materials and methods: Results: Female patient, 69 years old, underwent endoscopic polypectomy of a rectal sessile polyp with 6 mm, in 2001. Histological report showed "intestinal mucosa with thick nodular configuration due to expansion of the submucosa by carcinoid structures". The proliferative index was not determined. Clinical, endoscopic and imagiologic follow-up showed no evidence of disease recurrence. In 2015, an abdominal MRI detected multiple liver metastases. Liver biopsy confirmed the diagnosis of NET metastasis, with Ki67=20%. Serum chromogranin A (CgA) was elevated (319/mL) and 68Ga-DOTANOC PET/CT showed liver and perirectal malignant lesions. She was treated with octreotide and later, chemotherapy with capecitabine and temozolamide was added, due to disease progression. She currently remains in treatment and assymptomatic, with partial response of liver metastasis and stabilization of pelvic lesions (CgA 131.4ng/mL). Conclusion: The risk of distant metastasis in rectal NETs of the rectum with less than 1cm is below 3%. This is a rare case, which highlights the importance of long-term follow-up. Keywords: neuroendocrine, recurrence
Yttrium-90 Radioembolization for Progressive Medullary Thyroid Carcinoma with Exclusive Liver Metastasis

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Introduction: Medullary thyroid carcinoma (MTC) is a well-differentiated neuroendocrine tumor and accounts for 5-10% of all thyroid cancers. Distant metastases frequently involve the liver and patient’s survival after diagnosis is around 20% at 10 years Aim(s): Report the efficacy of Yttrium90 radioembolization in a MTC with exclusive liver metastasis (LM) Materials and methods: Male patient, 62 years old, underwent total thyroidectomy and bilateral neck dissection in 2010. Histology showed MTC, with 3.5 cm and microscopic extra-thyroid extension, pT3N0. Postoperative levels of calcitonin (CT) were 47 pg/mL (<18.2 pg/mL) and CEA 4ng/mL (<3.4 ng/mL). An hereditary form of MTC was excluded Results: Increasing levels of CT (380 pg/mL) and CEA (31 ng/mL) in 2012 lead to detection of two LM. Both lesions were excised, but recurrence of disease occurred later that year. He underwent four thermoablation sessions in 2013/2014 and liver subsegmental hepatic resection in 2015. In 2016, abdominal MRI reported progressive and unresectable disease, with 17 LM (no extrahepatic disease), CT 968 pg/mL; CEA 64ng/mL. He underwent Yttrium90 radioembolization in 2016, with partial response and dramatic reduction of CT (24 pg/mL) and CEA (11 ng/mL) levels. The patient is now asymptomatic and with stable disease Conclusion: There are limited effective treatment options for patients with unresectable MTC LM. In this case, several modalities were carried out but Yttrium90 radioembolization was be the most effective Keywords: neuroendocrine, yttrium radioisotopes
Yttrium90 Radioembolization for Progressive Medullary Thyroid Carcinoma with Exclusive Liver Metastasis

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Follow-Up in Neuroendocrine Neoplasms: Can Chromogranin A Be the Cofounder?

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Introduction: Chromogranin A continues to be one of the most valuable markers for neuroendocrine tumors (NETs) however, it has several limitations. Aim(s): Describe the difficulties associated to the follow-up in a NET patient. Materials and methods: Case report of a patient with a midgut NET. Results: Male patient, 61 years old, with chronic renal disease (CRD), underwent right hemicolectomy owing to ileo-cecal valve lesion; histological result consistent with NET. Pre-operative staging: without metastatic disease on thoracic-abdominal CT; octreoscan with elevated expression of somatostatin receptors on ileo-cecal valve topography; CgA 32nmol/L (<6.0), NSE 14 ng/mL (<15.0). Anatomopathological examination of surgical specimen: well-differentiated G1 NET; mesenteric infiltration and metastization in 1 of 20 lymph nodes (T3N1Mx; AJCC-IIB; R0). After 3 years of stable disease, the patient presented CgA of 1173.8ng/mL (<85), with impaired CRD (Cr 4.42mg/dL) on dialysis. Three months later: CgA 1619.0 pg/mL and Calcitonin 26pg/mL (<10). In additional investigation, cervical-thoracic-abdominal CT and 68 Ga-PET rated negative for relapse. The patient maintained follow-up with clinical stability, showing in the last evaluation CgA 272.3ng/mL, Calcitonin 38pg/mL, NSE 12ng/mL (<15) and Cr 6.88mg/dL. Conclusion: Evaluation of CgA in end stage renal disease is not reliable. In NET patients, renal function should be carefully evaluated and ruled out the potential impact on the concentration of CgA. Keywords: neuroendocrine, follow-up, cga, renal disease
A Case Report of NET G1 of the Gallbladder

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Introduction: The SEER database has shown that gallbladder NET is 0.5% of all NET cases, and G1 cases are limited to 2% in the rare gallbladder NET cases. Aim(s): Here we experienced a rare case of G1 NET in the gallbladder, and report the clinical features of our case. Materials and methods: Case: The patient was 48 year-old man, incidentally pointed out a mass in the cystic duct. Dynamic CT scan showed a space-occupying lesion in the cystic duct. MRCP showed papillary lesion protruding into the cystic duct. Those scans showed no signs of invasive tumor, and the tumor was just localized within the cystic duct. FDG-PET showed no significant accumulation. Duct biopsy and bile cytology was negative for malignancy, but imaging analysis never excluded the malignant possibility. Results: We performed open extended cholecystectomy. The intraoperative ultrasound examination showed the localization of the tumor to be in the cystic duct with no signs of invasion. Intraoperative rapid pathology showed no tumor invasion to the residual tissue. Conclusion: Final pathological diagnosis was NET G1 (Ki-67 labeling index was 1%). Immunohistochemistry revealed the tumor was positive for SSTR2 and somatostatin, and negative for other hormones. Keywords: net g1, gallbladder
Portal Hypertension-Related Digestive Hemorrhage in Patients with Pancreatic Neuroendocrine Tumors

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Introduction: Pancreatic neuroendocrine tumors (pNET) can cause portal hypertension (PHT). Aim(s): Describe patients with pNET and PHT-related digestive hemorrhage (PHT-DH). Materials and methods: Monocentric retrospective study from 2003 to 2016 of all consecutive patients with pNET who had PHT-DH. PHT was defined on CT-scan by thrombosis or encasement of mesenteric, portal or splenic veins. Results: Among 350 pNET patients, 12 (3.4%) had PHT-DH. All pNET were well differentiated, 9 had liver metastases and 7 were progressive at time of PHT-DH. PHT was due to thrombosis of mesenteric (5), splenic (8) and/or portal (7) veins, of mesenterico-portal confluent (6), or of portal vein encasement (1). PHT-DH were consecutive to rupture of esophageal (8), gastric (2), duodenal (1) or jejunal (1) varices. No patient was receiving somatostatin analogs, 2 patients had B-blocker primary prophylaxis. PHT-DH due to esophageal or gastric varices were treated with ligation or glue obliteration and somatostatin analogs. Four patients had 1 to 3 PHT-DH recurrences. In 2 patients PHT-DH occurred under bevacizumab, which was interrupted for endoscopic treatment. Eight patients died, but none due to PHT-DH. 8.1 months on average after PHT-DH. Conclusion: PHT-DH due to mesenteric, portal and/or splenic thrombosis can occur in patients with pNET, mainly in a context of tumor progression, and may restrain anti-tumor treatment. Prophylactic endoscopic screening and treatment might be proposed to patients with progressive pNET and morphologic PHT. Keywords: portal hypertension.
Outstanding Response to Sunitinib in a Patient with Unresectable Retroperitoneal Paraganglioma


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Introduction: Pheochromocitomas and Paragangliomas (PCs/PGLs) are rare neuroendocrine tumors arising from the adrenal medulla and extra-adrenal ganglia. Around 30-40% of these neoplasms are genetically determined. PCs/PGLs arising from the sympathetic chain can synthesize bioactive amines leading to typical syndromes, in contrast to parasympathetic PGLs that are mainly non-secretory. Aim(s): To describe a case of locally advanced paragangliomas treated with Sunitinib and radical surgery

Materials and methods: A 51-year-old woman referred to our center in July 2014 for abdominal pain and weight loss. A CT scan showed a large lesion in the upper left section of abdomen of 18 cm. The mass displaced vascular structures and embraced pancreas. A CT-guided biopsy documented the presence of retroperitoneal PGL. SUTNET, a single arm, monocentric, phase II study, designed to investigate safety and activity of Sunitinib in advanced and/or unresectable PCs/PGLs, was ongoing in our institution. Patient was enrolled in December 2014. Sunitinib was administered at the standard dose of 50 mg/day (4-weeks-on/2-weeks-off). Due to hematological toxicity, after 16 cycles, dose was reduced to 37.5 mg. Results: On October 2016 an assessment of CT scan showed a partial response of the mass (8 cm). The patient underwent surgery. The lesion was radically resected and histology confirmed diagnosis of PGL

Conclusion: Treatment options in advanced and/or unresectable PCs/PGLs are limited. Sunitinib could be a promising therapeutic strategy. Keywords: paragangliomas, sunitinib
A Single Centre Analysis of the Management of Appendiceal Neuroendocrine Neoplasms (NENs) Including Goblet Cell Carcinoids (GCC)

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Introduction: Appendiceal neuroendocrine neoplasms (NENs) are usually diagnosed incidentally on histology following an appendicectomy. They include carcinoid tumours (appendiceal neuroendocrine tumours, NETs) and goblet cell carcinoids (GCC). GCC neoplasms are able to transform to an adenocarcinoma phenotype. Aim(s): To assess whether the management of appendiceal NENs, including surgical management is appropriate, according to the histology of the appendicectomy specimen. Materials and methods: A retrospective analysis of the prospectively kept NETs database was performed. The type, staging, size and Ki-67 index of appendiceal NETs, and outcomes of right hemicolecotomies (RHCs) was extracted. Results: The database contained 75 patients: 51 appendiceal NETs, 21 GCC, and unknown type in 3 patients. A completion RHC was performed in 24 patients: 8 patients had evidence of lymph node (LN) metastases, distant metastases or residual disease. 5 cases in the appendiceal NET group who had a completion RHC had a T stage of pT1b, and of these 2 patients had evidence of LN metastases. 2 of the 3 appendiceal NETs >2cm where a RHC was performed, more advanced disease was seen. Our data showed that GCCs are more aggressive, presenting at a later stage. Conclusion: Our results show that GCC are more aggressive than appendiceal NETs, and therefore a more aggressive surgical approach should be considered. The definite management in the appendiceal NET group that fall in the pT1 group, remains most challenging. Keywords: appendiceal neoplasm, neuroendocrine tumors
A Case Report of Bicaval Stents and Inferior Vena Cava Valve Implantation to Control Carcinoid Symptoms in Order to Safely Allow Surgical Valve Replacement

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Introduction: Surgery for severe tricuspid regurgitation (TR) is a high-risk procedure. Therefore transcatheter valve implantation into the vena cava can be performed as an attempt to reduce the complications and symptoms associated with this. Aim(s): To determine the success of transcatheter valve implantation to control carcinoid symptoms in a patient. Materials and methods: A 69-year-old female with a background of metastatic neuroendocrine tumour experienced symptomatic severe CHD despite being on a somatostatin analogue. The plan was for invasive treatment to control the effects of TR on the liver to enable an ablation procedure to the liver metastases to be performed later. Results: Two stents were implanted into the IVC and SVC and a 29mm S3 valve was deployed within the IVC stent. Prior to valve deployment, phasic pressure in the IVC was 32/20mmHg. Following valve deployment, the IVC pressure fell to 15/8mmHg. Venography confirmed only minor paravalvular regurgitation. The procedure was well tolerated. Following the procedure, the patient became very unstable and passed away as a result of severe carcinoid crisis. Conclusion: IVC valve implantation to control the effects of TR to enable treatment to the liver metastases to treat the carcinoid disease, was the most appropriate treatment option for our patient. More studies are required to target the outcomes of IVC valve implantation in those with CHD to evaluate whether this is the most appropriate management in this group of patients. Keywords: carcinoid heart disease, neuroendocrine tumors
Outcomes of Hepatobiliary Neuroendocrine Neoplasms Treated with Systemic Therapy: A Retrospective Analysis

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Introduction: Primary hepatobiliary neuroendocrine neoplasms (NEN) are rare. Knowledge about clinicopathological findings and treatment results of hepatobiliary NEN is limited. Aim(s): To identify clinicopathological findings of hepatobiliary NEN and outcomes after systemic therapy. Materials and methods: We retrospectively analyzed cases of pathologically diagnosed hepatobiliary NEN treated with systemic therapy between January 1, 1980 and July 22, 2016. We defined primary hepatic NENs as NENs localized to the liver or found in the liver and the lesion not being the primary focus. We defined NEC as a tumor that has a neuroendocrine carcinoma component regardless of adenocarcinoma components. Results: A total of 23 patients received systemic therapy. The most common treatment for NEC was etoposide/cisplatin (EP), followed by gemcitabine/cisplatin (GC), gemcitabine (GEM), and irinotecan/cisplatin (IP). The median time to disease progression from the start of systemic therapy was 28 and 4 months for primary hepatic NET and primary hepatobiliary NEC, respectively. In subgroup analysis according to treatment regimen, the median OS of patients treated with EP/IP and GEM/GC were 10 months and 13 months, respectively. Conclusion: Primary hepatic NET (G1/G2) had a better prognosis than primary hepatobiliary NEC as did NEN in other parts of the body. The favorable outcomes of primary hepatobiliary NEC treated with GEM/GC may be attributed to the high proportion of cases with adenocarcinoma components. Keywords: primary, hepatobiliary, neuroendocrine, neoplasm
Introduction: A 58-year-old woman was referred to our hospital for hepatic lesions and thickening of the walls of the stomach detected by abdominal CT scan. An upper GI endoscopy showed a lesion of the body of the stomach and the histopathologic exam documented a well differentiated NET. 68Ga-DOTATOC PET showed pathologic uptake in the stomach and in the liver (3 lesions). Circulating chromogranin A and gastrin were 596 ng/ml and 2283 pg/ml respectively.

Aim(s): Materials and methods: A total gastrectomy was performed with the aim to remove primary tumor and the source of hypergastrinemia. The intraoperative ultrasound of the liver documented 6 small liver metastasis. Final pathology report confirmed a diagnosis of well-differentiated NET G2 (WHO 2010), with a mitotic count 15/10 HPFs and Ki67 20%, stage pT3N1. Due to the negative immunostaining for gastrin and the presence of chronic atrophic gastritis, a diagnosis of a type I gastric carcinoid was made. Circulating gastrin normalized one month later.

Results: The abdominal CT scan and 68Ga-DOTATOC PET performed after 6 months showed a complete regression of liver metastasis subsequently confirmed by CT scan regularly performed every 6 months (last evaluation on October 2016; 48 months from surgery). During this period circulating gastrin was always in the normal range.

Conclusion: Our case demonstrates that, by removing the stomach, and the source of hypergastrinemia in type 1 gastric carcinoids, a complete disappearance of liver metastasis can occur.

Keywords: gastric, net, complete remission, gastrin
Case Study: Immunotherapy in a Young Adult with Atypical Neuroendocrine Tumour

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Introduction: Use of immunotherapy PD-1 antibody has emerged as a novel therapeutic option for treating multiple solid tumors. In the setting of neuroendocrine tumors (NETs), little is known. Currently, trials are underway investigating its use in high-grade NETs, but outcomes remain to be seen. Aim(s): Case report demonstrating the use of monotherapy PD-1 antibody Pembrolizumab in a patient with advanced NET. Materials and methods: A 39-\textsuperscript{yo} male diagnosed 11-years prior with local, atypical thymic carcinoid (Ki-67 of 11\%). Failing twice thymectomy, platinum based chemotherapy, mTOR inhibitors, and Lanreotide, referred to our tertiary center for young adults with rare tumours. His chief complaint was dyspnea secondary to significant tumour burden in the mediastinum. He also had multiple bony metastasis. After discussion with the patient, decision was undertaken to start Pembrolizumab monotherapy. Results: After 5 cycles of Pembrolizumab, patient had a radiological and biochemical response. His re-staging PET/CT scan showed stable size with regression of all SUV values. Chromogranin A remains stable. Clinically, the patient's dyspnea improved significantly. Conclusion: Thymic NETs are the least common amongst primary thymic malignancies (2-5\%). Our case highlights the challenges in treating this atypical disease and the potential role for use of PD-1 antibody in NETs with moderately differentiated tumours. Further trials of immunotherapy treatments in NETs are eagerly awaited. Keywords: thymic neuroendocrine tumour, pembrolizumab, atypical carcinoid, nets
A Rare Case of Ectopic Cushing’s Syndrome

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Introduction: Cushing’s syndrome has an incidence of 0.7 - 2.4 per million people per year. In 15% of cases, it’s associated with non-pituitary tumors secreting ACTH. Pheochromocytoma accounts for 5% of ectopic ACTH secretion. Aim(s): - Materials and methods: - Results: A 65 year old female patient was admitted to hospital due to severe muscle and generalized weakness, shortness of breath and suppurated ulcers. Blood panel showed glucose levels of 16.3 mmol/L, Na - 140.9 mmol/L, K - 1.5 mmol/L. CT angiography revealed a PE in the upper lobe of the right lung and a pathological node 7x6.2 cm in diameter in the left adrenal gland, which was characteristic of a non-adenoma. ACTH was 152 pg/mL. Catecholamines were within normal range, and cortisol in 24 hour urine was 3962 nmol/24h. An MRI of the head showed no signs of a pituitary adenoma. The left adrenal gland was surgically removed. Pathohistological examination revealed a pheochromocytoma with a PASS score of 11 points, which proves a malignant biological potential. Levels of ACTH were evaluated again after the surgery and were within normal range – 33.2 pg/mL. Conclusion: The most likely diagnosis after the examination was a malignant ACTH secreting pheochromocytoma. Data from large series of patients with ectopic ACTH reveal that the most common cause is a bronchial carcinoid. Our case report demonstrates utmost importance of interpretation of clinical, biochemical, and radiological investigation in establishing the correct underlying cause of Cushing’s syndrome. Keywords: malignant pheochromocytoma
Over Treatment Radionuclide Therapy (PRRT) of Metastatic Neuroendocrine Neoplasm (NEN) – A Case Report

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Introduction: Over treatment radionuclide therapy (PRRT) of metastatic neuroendocrine neoplasm (NEN). Aim(s): A 39-year-old male with NEN G2 of unknown primary site with metastases to liver and bones. Materials and methods: Since May 2011 patient with abdominal symptoms. CT revealed enlarged liver with metastases. In June 2011 consultation of specimens from metastatic lesions in liver (from laparoscopy) confirmed the diagnosis of NEN G2 Ki-67 up to 20%. NEN markers and another hormones were in reference values. 68Ga-DOTA-TATE PET/CT scan confirmed the presence of changes with increased expression of somatostatin receptors (SSTR) in the liver and in the skeletal system. Since June 2011 patient has begun treatment with a long-acting somatostatin analogues (SSA). Between 08.2011 and 08.2012 patient received 6 cycles of 90Y/177Lu DOTA-TATE (800 mCi). In April 2013, PET/CT with gallium showed significant regression. In April 2014 PET/CT with gallium showed new foci of increased tracer uptake. In 09.2014 treatment with CAPTEM combined with SSA was commenced. Stereotactic radiosurgery therapy of metastatic changes in brain was carried out (10.2014), but in performed chest CT progression of disease was identified. Between 07.2015 and 02.2016, 4 further cycles of 90Y/177Lu DOTA-TATE treatment were administered (800 mCi). Results: The response to the treatment was satisfactory. Quality of life has been significantly improved. Conclusion: This case confirms effectiveness of radionuclide therapy. Keywords: neuroendocrine neoplasm, metastases, radionuclide therapy
Clinicopathological Features and Survival Analysis of 98 Patients with Gastroenteropancreatic Neuroendocrine Neoplasms

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Introduction: To investigate the clinicopathological features and prognostic factors of 98 patients with gastrointestinal Pancreatic neuroendocrine tumors. Aim(s): So as to improve our understanding and diagnosis and treatment level of GEP-NENs. Materials and methods: Data of 98 patients with gastrointestinal pancreatic neuroendocrine tumors were collected from January 2008 to June 2016 in Xinjiang Tumor Hospital. Their clinical manifestations, pathological features and survival were retrospectively analyzed. Results: There were 98 cases (67 males and 31 females) with a mean age of (54.5 ± 12.8) years. The incidence of the disease was most common in stomach (33/98, 33.7%), followed by rectum (31/98, 31.6%). The tumor size ranged from 0.2 cm to 9.2 cm (mean: 1.2 cm). The mean follow-up time was 18 months (range 1-10 months). The 1, 3 and 5 year overall survival rates were 93.8%, 80.6% and 66.1%, respectively. Univariate analysis showed that tumor location, size, grade, lymph node metastasis, distant metastasis and surgical methods were poor prognostic factors. Multivariate analysis did not reveal any independent risk factors. Conclusion: Gastrointestinal pancreatic neuroendocrine tumor is a rare disease, the clinical manifestations are not typical, the most common place is the stomach, mostly high-grade malignancy, followed by the more common in the rectum, mostly low-grade malignancies. Gastrointestinal pancreatic neuroendocrine tumors to surgical treatment based. Keywords: neuroendocrine neoplasms, clinical, pathology, prognosis
Acute Somatostatin Analog Suppression Test in a Patient with Thyrotropin-secreting Pituitary Macroadenoma

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Introduction: Thyrotropin-secreting pituitary adenomas are rare and often plurihormonal tumours. The long-acting somatostatin analogues (SSA) are effective in cases not cured after surgery. Aim(s): To assess TSH and FT4 response to acute octreotide administration. Materials and methods: We report a 39-year-old woman with a TSH-secreting pituitary adenoma. Results: The patient presented with bradimenorrhoea. There were no signs of thyrotoxicosis or acromegaly, no galactorrhoea. There was no family history of resistance to thyroid hormone’s syndrome. Thyroid function tests revealed mildly increased FT4 (26.4 pmol/l) with increased TSH (6.94 mIU/l). TPO antibodies were positive, TRAb were negative. Acute octreotide supression test (hourly TSH, FT4 measurements for 6 hours after 100 micrograms subcutaneous octreotide) showed a decrease in both TSH levels (3.7 mIU/l) and FT4 levels (20.5 pmol/l) at 4 hours after injection. Pituitary function assessment showed gonadotroph insufficiency; IGF1, prolactin, 8 a.m serum cortisol after 1 mg dexamethasone overnight test were normal. Computed tomography showed a 2.6/3.2 cm pituitary macroadenoma wth suprasellar extension and left cavernous sinus invasion. Transsphenoidal adenomectomy was performed. Immunohistochemistry confirmed a TSH secreting pituitary neuroendocrine tumor. Conclusion: Acute octreotide suppression test could be performed in thyrotropinoma patients, but further studies are needed to prove if there is a predictive value for long-term response to SSA. Keywords: octreotide, thyrotropinoma
A Successful Case of Controlling the Multiple Distant Metastasis of Pancreatic G2 NET with Local Therapy Combined with Systemic Pharmacotherapy

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Introduction: Several systemic pharmacotherapies could be applied to multiple metastatic pancreatic neuroendocrine tumor (PNET). However, we have not determined how to coordinate 'local' therapy such as salvage surgery and transarterial chemoembolization with systemic pharmacotherapies for these multiple metastatic PNET. Aim(s): To discuss the desirable combination of local therapy with systemic pharmacotherapy. Materials and methods: We report a successful case of controlling multiple liver metastases with lymphnode metastases of Grade2 PNET treated with combination of local and systemic therapy. Results: Case; 61 years old male was found to have a tumor of 12 cm diameter in the pancreatic tail. Distal pancreatectomy was performed and the diagnosis was NET G2. Two months after the operation, multiple liver metastases were detected by CT. He was treated with partial heptatectomy with octreotide. After 2 years of no recurrence, he had again multiple liver metastases with para-aortic lymphnode swelling. We performed trans-arterial chemoembolization (TACE) to control the liver metastasis, and resection of the para-aortic lymphnode metastasis in addition to octreotide treatment. Distant metastasis is now under control with octreotide alone for 2 years without any growing metastatic lesions. Conclusion: The disease course of this patient suggests that the combination of local therapy with systemic pharmacotherapy could improve survival of the metastatic NET patient. Keywords: pnet, salvage surgery, tace
Introduction: The slow-growing character of neuroendocrine tumors (NET) makes it difficult to assess treatment impact on tumor growth. Aim(s): Tumor growth rate (TGR) could be a new way to evaluate tumor dynamics in NET. Materials and methods: This retrospective case-series analysis was performed on 3 patients in Belgium (ages 80 [P1, male], 78 [P2, male] and 69 years [P3, female]) with lung NET stabilized on lanreotide Autogel (LAN, 120 mg/month). Tumor lesions at LAN therapy start (baseline) and after 78 (P1), 46 (P2) and 38 months (P3) were identified by computed tomography (CT) and measured according to RECIST 1.0. TGR (% change in tumor volume/month) was calculated from the sum of the longest diameters (SLDs) of the target lesions before and after LAN therapy start. Analyses are descriptive. Results: At baseline, all patients had well differentiated lung NET (Ki-67 <2%). Target lesion SLDs were 16.6, 54.9 and 53.3 mm, respectively, at baseline, versus 16.3, 51.4 and 52.0 mm after 78, 46 and 38 months of LAN therapy; all were classified as stable disease (SD) according to RECIST 1.0 (1.8%, 6.4% and 2.4% decrease in tumor size). TGRs were 0.0% (P1), -0.2% (P2) and -0.1% (P3). Conclusion: TGR assessment indicated that 2 of the 3 NET regressed whereas all 3 NET were classified as SD according to RECIST 1.0. Our results also suggest an anti-proliferative effect of LAN 120 mg/month in lung NET, but this needs to be confirmed in clinical studies. Industry sponsored. Keywords: nonfunctional lung neuroendocrine tumors, lanreotide, tumor growth, case-series
Sporadic Panglandular Non-Functioning pNET: New Entities? A Case Series

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Introduction: Sporadic panglandular pancreatic neuroendocrine tumors (PanNETs) have never been described yet. Aim(s): To report pathological features of sporadic PanNETs with involvement of the entire pancreatic gland. Materials and methods: The Institutional database of resected PanNET from 2006 to 2016 was investigated and three cases were retrieved. Clinical data were acquired and histological slides were revised. MEN-1 cases were excluded. Results: Three females (mean age 41y, range 36-46) were included. In 1 case pre-operative CT-Scan showed multiple nodulations (nodular pattern), whereas a diffusely increased pancreatic gland volume was observed in the remaining 2 cases (diffuse pattern). One patient per group was submitted to combined 68Ga- and 18FDG-PET/CT. In the nodular pattern 18FDG showed nonspecific uptake whereas 68Ga-PET/CT a focal enhancement within the nodulations. In the diffuse pattern both nuclear imaging showed a homogenous uptake in the whole gland. All patients underwent total splenopancreatectomy. The gross pathological examination confirmed two different patterns. In the microscopic analysis they shared a low grade (Ki67 <2%) and a local aggressive behavior with multiple nodal metastasis and microscopic local invasion (perineural, vascular and peripancreatic fat). Conclusion: Sporadic panNETs with panglandular pancreatic involvement are rare entities. We have still to clarify the correlation between histopathological features and biological behavior with a long-term follow up. Keywords: panglandular, pan nets, sporadic.
Videoconsultation during Follow-Up Care of Patients with a Neuroendocrine Tumor

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Introduction: Patients with a neuroendocrine tumor (NET) are increasingly treated in expert centers leading to longer travel times for medical consultations. Videoconsultation (VC) potentially allows remote guidance of patients. Aim(s): The primary aim of this study is to assess feasibility of VC during follow-up care of NET patients. Materials and methods: Twenty clinical stable patients received two VCs during follow-up care. Feasibility was assessed by calculation of participation/dropout rate and safety. Satisfaction questionnaires were filled out by patients and physicians. VC time, patient-reported travel time for an outpatient clinic visit and preference for type of consultation were noted. Results: Participation rate was 84% and 23% of the patients terminated the study prematurely. No safety concerns were reported. Median score for satisfaction of patients and physicians were 4.6 (range 3.3-4.9, 5-point Likert scale) and 4.0 (range 3.5-4.9) respectively, indicating high satisfaction with VC. Technical problems leading to prolonged connection time and impaired audio/video quality were reported by 55% and 40% of the patients and physicians respectively. Median VC time was 13 minutes (range 9-25). Patient-reported travel time to the outpatient clinic was 240 minutes (range 100-390). Sixty percent of the patients preferred VC. Conclusion: VC during follow-up care of clinical stable NET patients is feasible. Patients’ and physicians’ satisfaction with VC is high, but can be improved by technical support. Keywords: net, videoconsultation, telemedicine
External Beam Radiotherapy (EBRT) in the Treatment of Gastroenteropancreatic Neuroendocrine Tumors: A Systematic Review

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Introduction: EBRT is infrequently used to treat GEPNETS. Aim(s): To systematically review the evidence for EBRT in this setting. Materials and methods: Major databases and conference abstracts underwent dual independent review. Eligible studies included ≥ 5 patients treated with contemporary EBRT techniques for GEPNETs. The primary endpoint was local control. Results: Of 11 included studies (all retrospective), 7 investigated pancreatic NETs (PNET, 100 patients, 14% G3, 42% with chemotherapy) and four studies investigated Gastroenteric NET (GE-NET, 84 patients, 14% G3). Trials investigating PNETs administered a median of 50.4Gy via 3D-CRT and IMRT. EBRT was given with neoadjuvant or adjuvant intent in 56 patients with recurrence rate 15%. The response rate for 44 patients not undergoing surgery, the radiological response rate was 46%. Grade 3+ toxicity rates were 11% (acute) and 4% (late). Median distant recurrence-free survival ranged from 12-24 months, and overall survival (OS) from 24-56 months. 12 patients with GE-NET received RT to the primary tumour (all anorectal NECs) and 72 to metastases (34 bone, 27 brain, 11 soft tissue). Only one study reported dose at median of 50Gy. Local and distant control were poorly reported. OS ranged from 9-19 months. No GE-NET studies reported toxicity outcomes. Conclusion: EBRT appears to be well tolerated in selected pNET patients with encouraging efficacy. Outcomes from EBRT in metastatic NETS are not well reported. More studies are required to better define the role of EBRT in NETs. Keywords: ebtr, review
Pilot Electronic Survey to Locate Nurses Caring for NET Patients in Europe

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Introduction: There is an assumed variance in the roles nurses have in looking after NET patients, and the different levels of knowledge. Aim(s): The European Neuroendocrine Tumour society- Nurse Group wanted to locate nurses who take care for NET patients, and to explore their educational needs.

Materials and methods: A pilot study was created by developing a survey in English. This was mailed to the ENETs and UKINETs group; all healthcare professionals. A second, follow up survey was developed on the basis of the pilot study. Results: 36 responses, from UK, Norway, Sweden, Belgium, The Netherlands and Australia. 91% treated NETs, 93% had a nurse within their team. Role of the nurse varied hugely; most common was the support of patients, followed by contact nurse and outpatient clinic. Other roles included administration of injections and chemotherapy, research and clinical trial nurse, PRRT support and looking after hospitalised patients. The speciality that nurses worked within also varied; the most common was oncology, endocrinology and surgery. Nurses were also based in nuclear medicine, gastroenterology, lung and internal medicine teams. Conclusion: The findings of this pilot survey have been interesting and useful to help us target areas for our follow up survey. The second survey asks specific questions directly to the nurse regarding the role, education needs and access to education. This has been translated into French, German, Spanish, Dutch and Swedish, and is to be launched in January 2017. Keywords: nurse, neuroendocrine, education, survey
Neuroendocrine Tumors: A Retrospective Analysis in a Single Algerien Institution

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Introduction: Neuroendocrine tumors (NETs) are heterogeneous group of tumors. Aim(s): To evaluate clinical histopathological characteristics, treatments and outcomes of patients, in our single institute experience during the last 5 years. Materials and methods: All grade and sites of neuroendocrine tumors diagnosed from February 2011 to November 2016 were included. Small cell lung cancer was excluded. Results: 95 patients, 48 femals and 47 males. Median age was 53.6 years (23 to 85). 81% of patients had ECOG PS <2. Primary tumour sites were pancreatic 19%, small intestine 19%, jejunoileal 17%, gastric 8%, lung 9%, appendiceal 4%, colorectal 5%, unknown 11% with one case of prostatic, thymus and breast NET. 51.4% of patients had well differentiated morphology and 17.7% had neuroendocrine carcinoma. Ki 67 was superior to 20% in 12% of patient. 26% of patients presented carcinoid syndrome. 62.1% had distant disease, metastases in 79% in the liver, 12.6% locally advanced, 25.3% localized. Surgery was used in 51% with 18% on the liver metastasis. First line somatostatin analogue was administrated in 37% of patients, targeted therapy in 10.4% and chemotherapy in 29.3% of patients. Median progression free survival was 9 months, five year overall survival was 78.5%. Conclusion: Neuroendocrine tumors are heterogeneous diseases, with different behaviors. Each patient deserves personalized treatment. Keywords: neuroendocrine tumors
A Prospective Service Evaluation of Systematic Gastroenterological Assessment and Management on Patients with Neuroendocrine Tumours in South East Wales

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Introduction: Patients with NETs can experience gastrointestinal (GI) symptoms including diarrhoea, steatorrhoea and urgency. Aim(s): This prospective study evaluates the impact of GI assessment, investigation and management on quality of life (QOL) and GI symptoms upon establishing gastroenterology services to an endocrine/oncology NET service. Materials and methods: Patients with a proven NET referred to the GI NET clinic in South East Wales were prospectively selected. Patients completed 2 questionnaires at baseline: gastrointestinal symptom rating scale (GSRS) and the GINET21 questionnaire. After GI investigation and management, patients were asked to complete questionnaires again. Results: 20/57 patients completed GI management and repeat questionnaires. 75% had grade 1 NETs. 90% had a small bowel primary; all had metastases. 80% had bile acid malabsorption. Only 17% had abnormal faecal elastase despite steatorrhoea. 19 patients were commenced on either creon or colesevelam. 62% of patients has small intestinal bacterial overgrowth, 50% requiring antibiotics. There was a median of 6 months between questionnaires. After GI management, there was an improvement of impact of bowel symptoms on QOL with median decrease of 3 points on a 10 point scale. There was an improvement of QoL scores with a median increase of 1 point and a reduction of steatorrhoea, cramps, and faecal urgency scores. Conclusion: Gastroenterology assessment, investigation and management appear to improve QoL and GI symptom severity in patients with GEP-NETs Keywords: quality of life, diarrhea
Intraoperative Carcinoid Syndrome during Small-Bowel NET Surgery: Description, Prevalence and Risk Factors

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Introduction: Few studies on intraoperative carcinoid syndrome (ioCS) are available. Aim(s): Aims were to describe, define ioCS diagnosis criteria and evaluate ioCS risk factors. Materials and methods: We retrospectively analyzed patients operated for small-bowel (SB) NET in our ENETS excellence center (2007-2015) receiving preoperative continuous octreotide (40 or 80 µg.h⁻¹ according to the presence of liver metastases or prior CS). ioCS was defined as highly-probable (rapid arterial blood pressure changes ≥ 40% without surgical/anesthetic reasons and regressive ≥ 20% after octreotide injection), probable (one criteria missing) or suspected (octreotide injection for manifestation not meeting criteria of highly-probable and probable ioCS).

Results: 81 patients (liver metastases: 73%, prior CS: 60%, carcinoid heart disease: 9%) were included. 139 ioCs occurred in 45 (55%) patients: 45 highly-probable, 67 probable and 27 suspected. ioCS was hypertensive (91%) or hypotensive accesses (29%). No factors, including vasopressor use, were significantly associated with ioCS occurrence. All surgeries were completed and one patient died from cardiac failure 3 days after surgery. Conclusion: After preoperative continuous octreotide infusion, ioCS were mainly hypertensive ones. No ioCS risk factors, included vasopressor use, were identified suggesting the relevance of a standardized octreotide prophylaxis protocol. We propose a new definition of ioCS, which should be prospectively validated. Keywords: nets, carcinoid syndrome, intraoperative, octreotide
On-going Evaluation of The Clinical Utility of the Health-Related Quality-Of-Life (HRQoL) QLQ-GINET21 Questionnaire (QNR) in the Treatment of Patients (pts) with Gastrointestinal (GI) Neuroendocrine Tumours (NETs).

QUALINETS Study

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Introduction: Outcome measures reported by pts help to weigh benefit/effect of a therapy on quality of life (QoL), provided that their utility in clinical practice is proved. There are few QoL QNRs for pts with NETs, like QLQ-GINET21, with 21 items assessing muscle/bone pain, body image, information, sexual function, symptoms, social function and disease-related concerns. Aim(s): QUALINETS study aims to assess QLQ-GINET21 utility in making clinical and therapeutic decisions in routine clinical practice. Materials and methods: QUALINETS is a non-interventional, cross-sectional, multicenter study, currently conducted in routine clinical practice by 37 specialists from outpatient clinics at Spanish and Portuguese public hospitals. Pts must be 18 years or older, have diagnosis of GI-NETs, and complete QLQ-C30 and QLQ-GINET21 QNRs. Results: For all pts, doctors complete an ad hoc survey on QLQ-GINET21 utility with 14 items, 5 answer choices (0-4) and 3 dimensions: utility related to therapeutic and clinical decisions; to doctor–patient communication; and to QNRs own characteristics. Endpoints: percentage of pts (and 95% CI) for whom utility is low, moderate or high; HRQoL evaluation; and relationship between patient's health status and clinical variables with QLQ-GINET21 utility. The study, industry sponsored, aims to recruit 200 pts (NCT02853422). Conclusion: This study will assess QLQ-GINET21 utility in making clinical and therapeutic decisions. It is currently recruiting pts (110/200). Keywords: neuroendocrine tumors, qol, qlq-ginet21, utility
What Matters Most? An Exploration of Decision Criteria Considered by Patients with GEP-NET and Physicians Using Holistic Multi-Criteria Decision Analysis

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Introduction: Patient-centered care means identifying what matters most through shared decision making. EVIDEM provides an MCDA platform to explore decision criteria and tradeoffs. Aim(s): We developed a holistic decision support framework to identify preferences of patients and physicians in the management of unresectable, well- or moderately differentiated non-functioning GEP-NET. Materials and methods: Design of the framework was led by EVIDEM structure, literature review and insights from a Chatham-house panel of physicians and patients. During a second panel, 5 patients and 6 physicians weighed criteria using Hierarchical Point Allocation and Direct Rating Scale (DRS, sensitivity analysis). Insights were collected in discussions and individually. Results: The framework included 6 domains: Outcomes of intervention; Type of benefit; Need; Costs & constraints; Knowledge and Feasibility. Of the 30 (sub)criteria, 26 were considered by more than 90% of participants. Criteria weights were widely distributed reflecting differences in what matters most. On average, highest weights were given to Effectiveness (0.18±SD0.12 on total of 1), Disease severity (0.12±0.08), Safety (0.10±0.09), Type of therapeutic benefit (0.10±0.08) and Quality of evidence (0.09±0.06). Most important Effectiveness criteria were Overall and Progression-free survival. DRS gave similar results. Conclusion: Many aspects are considered by patients and physicians. Holistic MCDA reveals and structures the complexity of decision making. Keywords: mcda, decision making, gep-net, evidem
The Role of Hepatic Trans-Arterial Chemoembolization in Metastatic Medullary Thyroid Carcinoma: A Specialist Center Experience and Review of the Literature

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Introduction: Liver metastases are relatively common in patients with metastatic medullary thyroid carcinoma (MTC), carrying a negative impact on disease prognosis. The options for selective therapy of liver metastases in MTC patients are limited to catheter guided procedures such as trans-arterial chemoembolization (TACE). Data regarding the effectiveness and safety of this procedure in MTC is limited. Aim(s): To explore the clinical outcome, survival and safety profile of TACE for liver metastases in a group of MTC patients. Materials and methods: Retrospective case series of patients treated at a single tertiary university medical centre from 2005 to 2015. Results: Seven consecutive patients (mean age 64.5±10.9 years, 5 female) with histologically confirmed MTC with liver metastases were included. Metastatic involvement of the liver was less than 50% of the liver volume in all patients. The median size of the largest liver lesion was 40±6.9 mm. The patients underwent in total 20 sessions of TACE. Clinical improvement as well as tumor response (PR) were observed in all patients. The median time to tumor progression was 38 months (range 8-126). Three patients were still alive at the end of the follow-up period (a median overall survival rate of 57 ± 44 months). Conclusion: TACE in MTC patients with hepatic metastases is usually well tolerated and induces both clinical improvement and tumor response for prolonged periods of time in the majority of patients. Keywords: tace, mtc, liver metastasis
NeuroEndocrine Tumors of the Ampullary Region: A Rare Challenging Entity

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Introduction: NeuroEndocrine Tumors (NETs) of the ampulla of Vater are rare. Aim(s): To identify clinical presentation, treatment and prognosis of ampullary NETs. Materials and methods: We reviewed our experience in ampullary NETs from January 2007 to December 2015. Follow up (FU) to October 2016. Results: Among 169 pancreatico-duodenal NETs observed in our Unit in the last 9 years, four were NETs of the ampullary region (2.4%). 1 M/3 F, averaging 58.2 years (range 51-64). None of the patients showed positivity of endocrine markers and hormones at preoperative blood examinations. Median tumor size was 1.5 cm (range 0.1-2.5), and only one patient had a lymph node metastasis. Surgery: 2 pancreatico-duodenectomy (one performed in pancreatic cancer, with incidental finding of a non-functioning microNET), one ampullectomy and one enucleation. Two patients had a previous cholecystectomy, and were discovered to be somatostatinomas at immunohistochemical analysis; the others were non-functioning (NF) tumors. Two patients had a well-differentiated NET infiltrating surrounding structures or with lymph node metastasis (3/4 were G1), but none had a disease recurrence, and all but one (who died for pancreatic cancer) are alive after a median FU of 94.5 months (range 23-114). Conclusion: In our series, ampullary NETs seemed to be associated with a good prognosis, even if they were malignant NETs and an enucleation/ampullectomy could be performed. Keywords: gastroenteropancreatic neuroendocrine tumors, ampulla of vater
Optimising Followup after Complete Surgical Resection of Gastrointestinal Neuroendocrine Tumours- A Delphi Process to Produce Expert Consensus in an Area Lacking Clinical Evidence


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Introduction: Optimal follow-up for completely resected GI-NETS has not been well defined, with heterogeneity in awareness and application of existing guidelines. Aim(s): To investigate follow-up in GI-NETs using RAND/UCLA appropriateness methodology (RAM). Materials and methods: A multidisciplinary expert panel (n=18) scored 193 follow up care scenarios for GI-NETS using an online survey. Appropriateness of schedules and investigations for follow up were scored from 1 to 9. Median appropriateness scores were considered. Consensus was reached when 75% scored the scenario similarly. Results: Significant variation in followup duration and intensity existed, particularly beyond five years. For both Grade 1 & 2 tumours, followup frequency was impacted by nodal status, size and time since resection. Regardless of site, grade, tumour size or nodal status, cross sectional imaging and blood/urine-based biomarkers were scored as appropriate, whereas uncertainty in appropriateness was recorded for functional imaging. Fully resected, Grade 1 appendiceal NET, size <1cm was deemed appropriate to never follow up; but if 1-2 cm, there was uncertainty about frequency but certainty in the use of CT and biomarkers. Fully resected, Grade 1, T1 rectal NET was scored appropriate to followup once at 12 months with sigmoidoscopy, then discharge from followup. Conclusion: Using RAM, we describe appropriate followup frequency and necessary tests for follow up care of patients with fully resected GI-NETS. Areas of uncertainty requiring more study were identified. Keywords: ram, net
Patient-Reported Preferences in Treatments Approved in Neuroendocrine Tumors: A National Survey from the French Group of Endocrine Tumors


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Introduction: Patients with advanced neuroendocrine tumors (NETs) benefit from an increasing number of treatments. The patient’s preference could help physicians to choose among these options. Aim(s): Our patient-reported outcome survey aims to compare the perceived tolerance of treatments approved in NET patients. Materials and methods: Patients with advanced NETs treated by at least 3 different treatments were eligible. Patients evaluated their perceived tolerance from 1 (good) to 5 (poor) for each received treatment. Referent physician confirmed the type and ranking over time of each treatment. Results: 54 patients evaluated 246 treatments. The only factor associated with poor perceived tolerance was female gender. Median toxicity scores increased from 1 (somatostatin analogs, peptide receptor radionuclide therapy (PRRT)), 2 (surgeries, radiofrequency ablation and oral chemotherapy), 3 (interferon and everolimus), to 4 (liver embolization, sunitinib and intravenous chemotherapy). In taking somatostatin analogs as reference, the odd ratios for poor perceived tolerance were 1.7 [0.6–5.1] for oral chemotherapy, 2.2 [0.9–5.3] for primary tumor surgery, 2.4 [0.6–9.5] for radiofrequency ablation, 2.8 [1.1–7.3] for metastasis surgery, 3.4 [1.4–7.9] for everolimus, 3.7 [1.6–8.5] for liver embolization, 4.9 [2.2–10.7] for intravenous chemotherapy and 5.9 [2.6–13.1] for sunitinib. PRRT had a negative odd ratio.

Conclusion: Our retrospective analysis suggests that perceived tolerance differs in between therapeutic options. Keywords: neuroendocrine tumor, toxicity, prog...
Quality of Life in Patients with Multiple Endocrine Neoplasia Type I (MEN1): Results from the Dutch MEN1 Study Group

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Introduction: Multiple Endocrine neoplasia type 1 (MEN1) is a hereditary tumor syndrome, characterized by an increased lifetime risk of benign and malignant endocrine tumors in various organs. Data on quality of life (QoL) in patients with MEN1 are scarce, whereas QoL is considered an important treatment outcome. Aim(s): The primary aim was to evaluate the presence of MEN1-related fear for disease occurrence in MEN1 patients. The secondary aim was to assess the impact of MEN1 on health related QoL (HRQoL) and to identify variables that were significantly related to reduced QoL and cancer worry. Materials and methods: A cross-sectional study was performed in which MEN1 patients completed the Short-Form 36 Health Related QoL and the Cancer Worry Scale. Results: 201 patients completed the questionnaire. The mean age was 47.7 (SD 1.0). A total of 101(57%) patients had a pancreatic neuroendocrine tumor. One third of patients never worried about their chances of developing a MEN1 related tumor. One third of patients never worried about their chances of developing a MEN1 related tumor. A percentage of 75% of patients had considerable worries about the need of surgery in the future. Patients who were unemployed had more cancer worries. In addition, patients who had a pNET had more worries than patients without pNETs. There was more worry about tumor occurrence in their children than in patients theirselves. Patients had significantly lower SF-36 HRQoL scores than the general Dutch population, except for the physical functioning subscale. Conclusion: Patients with MEN1 have considerable cancer worry and diminished HRQoL. Keywords: men1, qol