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16th Annual Meeting of the UK and Ireland Neuroendocrine Tumour Society 2018

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CONTENTS

16th Annual Meeting of the UK and Ireland Neuroendocrine Tumour Society 2018

Speaker Abstracts

Speaker Abstracts

Diagnostic and Management Challenges in NETs

NETS1

New pathology classification in GEP-NENs

Tu Vinh Luong
Department of Cellular Pathology, Royal Free London NHS Foundation Trust, London, UK.

The classification and nomenclature of neuroendocrine neoplasms (NENs) is complex, can be confusing and has undergone major changes over the last three decades, as illustrated by the evolution in classification of GEP-NENs by the WHO. The 4th edition of the WHO's classification of GEP-NENs was published in 2010. This edition is currently in use for gastrointestinal neuroendocrine neoplasm (GI-NEN) classification. The WHO 2010 classification introduced a strict separation between well-differentiated neoplasms (defined as NETs) and poorly differentiated neuroendocrine carcinomas (defined as NECs). NETs are, by definition, either grade G1 or G2 only and NECs are, by definition, always grade G3. There is **no** 'well-differentiated neuroendocrine carcinoma' in the WHO 2010 classification. Accumulating evidence strongly suggests that the G3 category of pancreatic neuroendocrine neoplasms (PanNENs), with Ki-67 > 20%, is a heterogeneous group and actually includes two different entities that profoundly differ in their biology, prognosis and molecular genetics: i) well-differentiated NET with an elevated proliferative rate; and ii) poorly differentiated NEC with small cell or large cell morphology. Based on this new evidence, in 2017, the WHO classification of the PanNENs applied the three tier grade system to the well-differentiated NENs, introducing the well-differentiated neuroendocrine neoplasm of high grade or NET G3 category. Further changes of the 2017 WHO Classification of PanNEN include the new definition of mixed tumour category as mixed neuroendocrine non-neuroendocrine neoplasm (MiNEN), replacing the previous term mixed adenoneuroendocrine carcinoma (MANEC). The new 2017 WHO Classification of PanNENs should now be used for PanNEN classification. Though not formally published by WHO yet, this new pancreatic NET G3 category and new term for mixed tumours MiNEN can be adopted for all other GI sites. The 5th edition of WHO classification of GI-NENs is expected to be published in 2019.

DOI: 10.1530/endoabs.60.NETS1

NETS2

Chemotherapy: "is this the end of an old friend"

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Chemotherapy has historically been the 'work horse' of medical oncology. An improved understanding of the biological behavious of neuroendocrine neoplasms has led to decision-making based on pathological characterisation of neuroendocrine neoplasms in to well-differentiated neuroendocrine tumours (NETs) vs poorly-differentiated neuroendocrine carcinomas (NECs). Platinum/etoposide has an established role in high-grade NECs with high responses, although these are often short-lived. There is a need to identify effective second-line treatment options through well-conducted prospective studies. In well-differentiated NETs, the use of streptozocin in combination with 5-FU or doxorubicin is being increasingly superseded by temozolomide with limited prospective randomised until the recent presentation of the E2211 study at ASCO 2018. This presentation will explore the current and future role of chemotherapy and how treatment decisions can be guided by the available evidence; areas of opportunity for further studies will also be highlighted.

DOI: 10.1530/endoabs.60.NETS2

NETS3

Medullary thyroid carcinoma: management challenges

Nick Reed
Glasgow, UK.

Medullar Thyroid cancer (MTC) is uncommon and a mixture of sporadic and familial. Surgery is the only curative treatment to date. Prophylactic surgery is required in the hereditary forms. No adjuvant post-operative treatment has demonstrated survival benefit. External radiotherapy may be used selectively. Calcitonin and CEA are used for post-operative monitoring of recurrence. At time of relapse consider whether there is a surgical option. The rate of doubling has prognostic value and helps to determine timing of intervention. Traditional chemotherapy is of very limited use. New targeted agents have shown considerable activity. Vandetanib and cabozantinib are the two approved agents. Specific RET antagonists are showing greater potential benefit Metastatic MTC is often very slow growing and indolent so do not rush in with systemic therapies. Patients should be managed by specialist teams with access to a CNS.

Synopsis of talk

Medullary thyroid cancer: management challenges

Medullary thyroid cancer (MTC) is uncommon and accounts for between 5 and 10% of all thyroid cancers. MTC may be hereditary as in MEN2 and FTC but there are sporadic forms although new technology identified. In familial forms prophylactic surgery is deployed. Patients are either diagnosed through genetic screening or present with a thyroid lump. Surgery is the only curative treatment to date. Selective use of adjuvant radiation may be considered for high risk cases such as positive margins and heavy nodal infiltrate. Post-operative monitoring is clinical and biochemical with measurement of CEA and Calcitonin. Many cases are indolent but monitoring the doubling time of Calcitonin gives prognostic information and helps to determine timing of intervention. When there is a relapse, determine if there is an opportunity to consider further surgical intervention. Many patients with metastatic disease have very slow growing metastases or may have negative imaging with elevated stable Calcitonin levels and these may be kept under surveillance for years. Intervention should only be considered for symptomatic progressive disease. Traditional chemotherapy has little value so the use of new targeted agents has developed rapidly. These are multi-targeted TKIs and the only two approved are vandetanib and cabozantinib although a number of others has shown clinical benefit. They appear to be of roughly equal efficacy so personal experience and familiarity with toxicities may determine which is used. New more specific ret pathway inhibitors (LOXO 292 and BLU 667) are reported to show significantly higher levels of activity and lower toxicity but have not progressed beyond phase 2 studies. Everolimus an mTOR pathway inhibitor may be of use, and radionuclide studies show some patients may benefit from PRRT using mIBG or Lutetium. Patients should be managed in specialist clinics with experience of managing MTC and with access to Clinical Nurse Specialists.

DOI: 10.1530/endoabs.60.NETS3

NETS4

Duodenal NETs: under (-over) treated?

Mohid Khan
Cardiff, Uk.

Duodenal neuroendocrine neoplasms (d-NENs) account for approximately 2% of all NENs, frequently encountered incidentally at endoscopy. They can be classified in a number of ways: ampullary/peri-ampullary and non-ampullary; gastrinomas, somatostatinomas, non-functional d-NENs, duodenal gangliocytic paragangliomas and high-grade poorly differentiated NECs. More than 90% arise in the 2st or 2nd part of the duodenum. ENETS guidelines suggest managing d-NENs according to size, with endoscopic resection of those less than 1 cm in diameter (if not peri-ampullary). Endoscopic Submuocsal Dissection generally achieves higher rate of radical resection than Endoscopic Mucosal Resection. d-NENs greater than 2 cm should undergo surgical resection especially if lymph node positive. d-NENs between 1 and 2 cm can be endoscopic or surgically resected. Those with metastatic disease can be managed similarly to metastatic disease in other areas, dependent on grade. However, the natural history of incidental d-NENs is unclear a lack of data in the literature, meaning some cases could be managed by observation/surveillance depending on individual patient factors.

DOI: 10.1530/endoabs.60.NETS4

NETS5

Nutrition support in GEP-NETs: an underestimated co-worker

Sheldon Cooper
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Gastroenteropancreatic Neuroendocrine Tumours (NETs) may lead to gastro-intestinal symptoms directly or as a result of their treatment, for example surgical resection and/or somatostatin analogues (SSA). When these symptoms become severe, patients may develop a reduced ability to successfully digest and absorb nutrients in the diet. This may be specific due the area of resection, e.g. vitamin B12, or secondary from medication, e.g. SSA induced pancreatic exocrine

insufficiency leading to fat soluble vitamin malabsorption, but more often this may affect a variety of macro- and micro-nutrients, and in severe cases electrolytes and hydration status. Identification of the aetiology of the symptoms leading to the loss of nutritional autonomy is vital to managing and improving the situation. Multi-disciplinary working between gastroenterologists (with a clinical nutrition interest), dietitians and the NET team is vital in maximising nutritional response. In extreme circumstances, resection may lead to short bowel syndrome and intestinal failure where the ability to digest and absorb the diet falls below a level that can sustain life. Whilst medical regimes to treat short bowel syndrome and oral nutritional support may help, home parenteral nutrition may be required. Whilst this raises a whole new level of complexity to care, it can be successfully employed with the Nutrition Support Team (NST), restoring both prognosis and quality of life.

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Bronchial NETs

NETS6

Abstract Unavailable.

NETS7

Abstract Unavailable.

NETS8

Abstract Unavailable.

NETS9

Abstract Unavailable.

NETS10

Surgical management of thoracic neuroendocrine tumours

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Regional Department of Thoracic Surgery, University Hospitals Birmingham, Birmingham, UK.

The management of neuroendocrine tumours involving the thoracic cavity has evolved over the past few years. However, there remains large variation in diagnosis, treatment and follow up of these patients. The lessons learnt from management of these tumours at other sites in the body have led to recommendation of radical resection of these tumours, while preserving the lung parenchyma. The surgical techniques for management of NET tumours and experience of Regional department of Thoracic Surgery will be discussed.

DOI: 10.1530/endoabs.60.NETS10

NETS11

Bronchial NETs: follow-up pathways: A lung physicians view

Seamus Grundy
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The predominant treatment modality for patients with bronchial neuro-endocrine tumours (excluding small cell lung cancer) is surgical. Despite this, disease can recur, in both local and metastatic form, even many years after treatment. The follow-up of patients after surgery should aim to improve clinical outcomes and avoid harm. Follow-up can be in the form of clinical review, biochemical tests and radiological imaging. The evidence base for the optimal form of follow up for these patients is currently limited. International Guidelines differ and are predominantly based on consensus opinion. Evidence to support current practice will be reviewed. Further, the potential to develop an evidence-based, risk-stratified approach to follow up will be discussed.

DOI: 10.1530/endoabs.60.NETS11

NETS12

Bronchial NETs

Wasat Mansoor
Manchester and Martyn Caplin, London, UK.

Well differentiated lung neuroendocrine tumours (WD lung NETS) are common NETs accounting for 25% of all the presenting neuroendocrine tumours. However, they are classified differently compared to GEP NETs, their mode of presentation; pattern of metastatic spread; associated syndromes, and how they respond to therapies are different from GEP NETs. They even present to a different group of specialists (respiratory physicians and thoracic surgeons) whereas the GEP NET patients traditionally present to GI specialists (gastroenterologists and GI surgeons) who are traditionally more closely aligned to the 'NET team'. It is therefore not unsurprising that the management pathways for WD lung NETs has historically developed differently from the GEP NETs. Literature and surveys indicate the there is a need to improve the WD Lung NET management pathway which has not developed at the same pace as that for GEP NETs. This session focuses on many aspects of the diagnostic and treatment pathway for WD Lung NETs and also examines how the follow up part of the general pathway is perceived by important members of the pathway: the respiratory physician, the thoracic surgeon and the NET physician.

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Challenging the Experts

NETS13

Abstract Unavailable.

NETS14

Abstract Unavailable.

NETS15

Abstract Unavailable.

NETS16

Abstract Unavailable.

NETS17

Abstract Unavailable.

NETS18

Abstract Unavailable.

NETS19

Abstract Unavailable.

Translational Science

NETS20

Immunotherapy in NETs

Nicola Fazio
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Immunotherapy in neuroendocrine neoplasms (NENs) has been investigating over the years, mainly with interferon-alpha-2b and oncolytic virus, without conclusive results. The new immune checkpoint inhibitors (IC-Is) are in an initial phase of investigation in NENs with no published study so far, apart from Merkel Cell Carcinoma (MCC). For this latter NEN Avelumab has been recently approved by the FDA and EMA in advanced disease irrespective of the line of treatment. From a biological standpoint low grade neuroendocrine tumors (NETs) do not represent the ideal setting for investigating IC-Is as they have been reported to have a low tumor mutational burden (TMB); by contrast high grade neuroendocrine carcinomas (NECs), mainly small cell lung and extra-lung NECs are potentially more responsive. Preliminary results from some studies with anti-PD-1 agents were presented at the main congresses over the latest two years, including pembrolizumab, PDR001, and JS001.The tumor population was selected on the basis of positivity for PD-L1 just in the pembrolizumab study, that was a cohort of the Keynote 028 phase II basket trial. Unfortunately the three studies included a very heterogeneous population, in terms of primary sites, tumor grade and histotypes. Overall response rate (RR) was 6% in pancreatic NETs and 12% in extra-pancreatic NETs in the pembrolizumab trial, however the primary endpoint threshold of significance is unknown. The PDR001 trial was a negative study, due to the unmet primary endpoint of 10% RR in the global population, although a 20% of RR was observed in the lung cohort. The preliminary results of the JS001 study showed a high RR, especially in NETs compared with NECs and in PD-L1 positive compared with negative neoplasms. At the ASCO 2018 congress negative results of pembrolizumab in a population of NECs were reported. So far results of IC-Is in NETs are difficult to be interpreted, considering the heterogeneity of the tumor population included, the lack of a central pathology review and design of the trials. While the publication of the presented trials is waited then combinations of different new immunotherapeutic agents or IC-Is and molecular targeted agents should be investigated in homogeneous populations of NETs.

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Plenary Speaker

NETS21

Abstract Unavailable.

Oral Communications

OC1

The proinflammatory molecule, VAP-1, is enriched in the stroma of midgut NETs and plaques of carcinoid heart disease valves

Vandana M Sagar[1,2], Desley AH Neil[1], Pantelitsa Papakyriacou[2], Tahir Shah[1], Boyang Liu[1], Gideon Hirschfield[2], Richard P Steeds[1], Shishir Shetty[2] & Christopher J Weston[2]
[1]Queen Elizabeth, Hospital Birmingham, Birmingham, UK; [2]Centre for Liver and Gastrointestinal Research, Birmingham, UK.

Background
Vascular adhesion protein-1 (VAP-1) is a novel driver of tissue inflammation and fibrosis and may contribute to fibrotic complications of neuroendocrine tumours (NETs). We studied the VAP-1 expression in midgut NETs, which are associated with desmoplasia, and carcinoid heart disease (CHD), a significant complication of metastatic midgut NETs.
Methods
Immunohistochemical analysis of paraffin-embedded midgut NETs and CHD valves were stained for VAP-1 and collagen I, with valves additionally stained for collagen III and CD31. VAP-1 expression was assessed semi-quantitatively. Circulating VAP-1 concentration was measured by Europium-based time resolved fluorescence in serum from NET-CHD positive patients ($n=7$), NET-CHD negative patients ($n=18$) and non-NET controls ($n=74$, metabolic syndrome but no evidence of liver disease).
Results
There was strong VAP-1 expression in the midgut NET stroma, in close association with collagen deposition (Spearman's correlation co-efficient 0.310, $P=0.281$). Increased VAP-1 expression was detected in CHD valves ($n=33$) compared to control valves ($n=6$, aortic/mitral degenerative disease), $P<0.001$. VAP-1 expression was not seen in control valves or chords but was seen within neo-vessels within the CHD valve and the plaque. VAP-1 expression increased with plaque maturity: increasing from myxoid to collagen to elastin rich areas. In myxoid areas, VAP-1 expression was confined to cells whilst increasing in the interstitium with maturity. Increased collagen I and collagen III expression was present in both groups but to a greater extent in CHD valves, with collagen III staining more selectively. Soluble VAP-1 was significantly elevated in patients with midgut NETs (median 562.5, IQR 438.8 – 697.3 ng/ml) compared to controls (median 256.0, IQR 212.0 – 308.0 ng/ml) $P<0.0001$. Patients with NET-CHD positive had a significantly higher concentration (median 691.0, IQR 684.0 – 854.0 ng/ml) than NET-CHD negative patients (median 511.0, IQR 411.3 – 583.8 ng/ml), $P<0.01$.
Conclusion
This is the first description of VAP-1 expression in midgut NETS and CHD. We found high circulating VAP-1 levels in NET patients, with the highest concentration seen in NET-CHD positive patients. VAP-1 expression was associated with a dense collagen and stroma network, including neovascularisation development in CHD. These studies implicate VAP-1 in the pathophysiology of midgut NETs, with potential utility as a stratification tool and a novel therapeutic target.

DOI: 10.1530/endoabs.60.OC1

OC2

Lanreotide depot/autogel before, during, and after peptide receptor radionuclide therapy (PRRT) in advanced neuroendocrine tumors (NETs): Data from the PRELUDE study

Vikas Prasad[1], Raj Srirajaskanthan[2], Christos Toumpanakis[3], Chiara Maria Grana[4], Sergio Baldari[5], Tahir Shah[6], Angela Lamarca[7], Frédéric Courbon[8], Klemens Scheidhauer[9], Eric Baudin[10], Xuan Mai Truong Thanh[11], Aude Houchard[11] & Lisa Bodei[12]
[1]Universitätsklinikum Ulm, Ulm, Germany; [2]Kings College Hospital, London, UK; [3]Neuroendocrine Tumour Unit, Royal Free Hospital, London, UK; [4]European Institute of Oncology, Milan, Italy; [5]University of Messina, Messina, Italy; [6]Queen Elizabeth Hospital Birmingham, Birmingham, UK; [7]The Christie NHS Foundation Trust, Manchester, UK; [8]IUCT-Oncopole, Toulouse, France; [9]Technical University Muenchen, Klinikum rd. Isar, Munich, Germany; [10]Institut Gustave Roussy, Villejuif, France; [11]Ipsen, Boulogne Billancourt, France; [12]Memorial Sloan Kettering Cancer Center, New York, NY, USA.

Background
PRRT, licensed for gastroenteropancreatic (GEP) NETs, has been used with somatostatin analogues such as lanreotide autogel (LAN). PRELUDE is the first international, multicentre retrospective study, with central radiology reading, to describe use of LAN with PRRT (LAN-PRRT) in advanced NETs.
Methods
PRELUDE (NCT02788578) was an international, retrospective, non-comparative analysis of medical records of patients receiving LAN with 177Lu-DOTATATE/DOTATOC, and 12-month LAN only follow-up. Four UK sites participated. Key inclusion criteria: metastatic/locally advanced, grade 1/2, somatostatin receptor positive GEP or lung NET, progressive disease (PD) in the year prior to LAN-PRRT start, ≥ 1 LAN injection 8 wks before the 1 LAN-PRRT cycle, continuous LAN use during LAN-PRRT, cumulative PRRT activity ≥ 500 mCi. Primary endpoint: progression-free survival (PFS) rate from day 1 of 1st cycle to the end of the last LAN-PRRT cycle (RECISTv1.1, centrally assessed). Secondary endpoints included best overall response (OR; RECISTv1.1), objective response rate (ORR), change from baseline in diarrhoea and flushing. Safety included incidence of nephro, hemato and hepatotoxicity; vomiting during infusion.
Results
Enrollment was terminated early (insufficient recruitment). Of 40 patients enrolled, 39 had GEP NET (incl.; ileum 33.3%, unknown origin 25.6%, right colon 20.5%, pancreas 10.3%); one had lung NET (full analysis set: GEP NET $n=23$, lung NET $n=1$). 30 patients enrolled were from the UK. Most patients with GEP NET had Ki67 $>$ 2-$\leq$20% (53.1%), global overall Krenning score (centrally assessed) grade 4 (70.4%), received 4 (17/23 patients) LAN-PRRT cycles, and 120 mg LAN (18/23) last dose before PRRT. Median (range) LAN exposure: 37.0 (13.2, 90.0) mo overall; 12.6 (6.1, 32.5) mo during LAN only follow-up. PFS rate [95% CI]: 91.7% [53.9–98.8]. Best OR (GEP NET): 34.8% partial response, 60.9% stable disease, 4.3% PD. ORR at time of last LAN-PRRT cycle [95% CI]: 27.3% [13.2; 48.2]. Most patients with GEP NET had stable/improved diarrhoea (15/15) and flushing (13/14). Few toxicities reported; no safety issues identified.
Conclusion
Effectiveness data were encouraging in this selected population. In clinical practice, LAN use is considered before, during, and after PRRT. This study was sponsored by Ipsen.

DOI: 10.1530/endoabs.60.OC2

OC3

PUnNETS (Prediction of Unknown Neuroendocrine Tumour Site) – a DNA methylation-based classifier

Alison M Berner[1], Christodoulos Pipinikas[1], Anna Karpathakis[1], Harpreet K Dibra[2], Ismail Moghul[1], Amy Webster[1], Tu Vinh Luong[3] & Christina Thirlwell[1,3]
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Neuroendocrine tumours (NETs) of unknown primary (UP-NETs) represent up to 22% of NETs. Primary site identification enables patients to access appropriate treatment but is not always possible by immunohistochemistry or imaging. Given the epigenetic dysregulation of NETs, we aimed to use methylation array data to determine UP-NET tissue-of-origin. DNA from formalin-fixed paraffin embedded tissue from 76 pancreatic NET (PanNETs) (54 training and 22 validation samples) and 53 small intestinal NET (SINETs) (43 training and 10 validation samples), were run on the Illumina 450K methylation array. Probe filtering and normalisation were performed, including removal of probes not on the Illumina EPIC array, to allow use with EPIC array samples. Differentially methylated probe (DMP) analysis was performed for PanNET and SINET training samples. Methylation values for these DMPs were used as input for an ensemble learning support vector machine (SVM) training algorithm with 70 ensembles and 250 bootstrap reanalyses. The resulting PUnNETS (Prediction of Unknown NET Site) classifier was then used to predict the tissue of origin for the validation samples. 594 DMPs with differential methylation $>40\%$, $P<0.001$, enabled separation of training samples by tissue of origin using hierarchical clustering and were used for classifier input. The PUnNETS classifier had an average accuracy of 100% in the training set and 98.75% in the test set (derived from multiple divisions of the training set). PUnNETS accurately predicted the tissue of origin for all 32 validation samples with confidences scores 68.6–100%. PUnNETS uses methylation array data to predict the tissue-of-origin UP-NETs with a high level of accuracy and following further validation has the potential to be used in clinical practice.

DOI: 10.1530/endoabs.60.OC3

Poster Presentations

P01

Functional or non-function pancreatic NET; Novel use of a flash glucose monitoring system

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High grade pancreatic NETs are usually non-functional. Here, we report a case of a patient with a high grade pancreatic NET, which was initially non-functional but became functional after chemotherapy. He was initiated on a flash glucose monitoring device (FreeStyle Libre®) avoiding the need for frequent capillary blood glucose monitoring. Using this novel approach, we demonstrated an improvement in his disabling hypoglycaemia with medical treatment. A 45-year-old professional athlete presented with abdominal pain and an urgent CT scan of the abdomen revealed a 4 cm tumour in the tail of the pancreas with multiple liver metastases. A liver biopsy confirmed a high-grade but differentiated tumour with a Ki67 index of 30–40% (G3). The patient was referred for chemotherapy (carboplatin/etoposide). During one hospital admission after chemotherapy, he was incidentally found to have hypoglycaemia (2.6 mmol/L) with an inappropriately normal insulin level of 61.0 pmol/L (reference range 17.8–173), along with a C peptide level of 1465 pmol/L (reference range 370–1470), and highly elevated proinsulin levels of 870 pmol/L (reference range 0–10). He initially required a continuous intravenous dextrose infusion to maintain euglycaemia and this was weaned slowly as he was simultaneously commenced on oral dexamethasone and diazoxide and later on a somatostatin analogue (lanreotide) with significant improvement of hypoglycaemia. He was discharged home with a Free Style Libre®. Periodic clinical follow-up and data download of his blood glucose profile demonstrated a significant improvement in hypoglycaemia. Interestingly, our patient did not report symptoms of hypoglycaemia at diagnosis but clearly developed hypoglycaemia later on. We hypothesize that initial chemotherapy, in this case, may have preferentially targeted high-grade tumour cells allowing for an expansion of low-grade cells that potentially contributed to the observed hyperinsulinaemia and functionality. To our knowledge, this phenomenon has never been reported before. Further, we have shown that a flash glucose monitoring normally reserved for patients with type 1 diabetes has clinical utility in the management of hypoglycaemia in the context of a neuroendocrine tumour.

DOI: 10.1530/endoabs.60.P01

P02

Overview of neuroendocrine patient demographics and outcomes in the Leicestershire region

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Neuroendocrine tumours (NETs) are rare cancers originating from neuroendocrine cells. The estimated prevalence is 35 per 100,000 people per year. A comparative review was conducted at the University Hospitals of Leicester (UHL) to determine the outcomes of treated neuroendocrine patients.

Methods

Patients were identified via pharmacy records of Lanreotide, from April 2009 – March 2018. Clinical data was obtained from hospital notes and histopathology reports were accessed electronically.

Results

During this period, 83 patients were treated. Most patients were Caucasian (87%) and male (57%). The median age at diagnosis was 60 years. At presentation, 86% of patients were symptomatic.The commonest primary site was small bowel (43%) followed by pancreas (25%). Most patients had metastatic disease at presentation (76%), mostly in the liver (86%). Where pathology was available, most tumours were classified as grade 1 (44%). Systemic treatment alone was the most common treatment, occurring in 38% of patients. After 1st line treatment, 86% required a treatment change. All 23 patients who had surgery alone went on to receive 2nd line treatment, with a progression free survival (PFS) of 61.8 months. When starting Lanreotide, the most common dose was 90 mg (51%) with a PFS of 28 months. Patients on 60 mg (21%) had a PFS of 34 months, and those receiving 120 mg (17%) had a PFS of 15 months. The Asian sub-population comprised 6% of patients, and 80% were diagnosed with a grade 2 tumour with liver metastases, and 60% had a Ki-67 index of over 5%. All Asian patients had Lanreotide as part of their primary treatment at 90 mg or above, with a PFS of 19 months.

Discussion

We found that treated NETs were grade 1 tumours, found in Caucasian males, presenting with symptomatic metastatic liver disease. In the smaller population of Asian patients, most NETs were grade 2. The median overall survival regardless of therapy was 59 months, and this fits with a recent review stating this varies from 24–68 months.

Conclusion

This study of UHL patients found that the demographics and outcomes of NETs were comparable to those found in recent studies.

DOI: 10.1530/endoabs.60.P02

P03

Second primary malignancies (SPMs) in patients with non-pulmonary well-differentiated neuroendocrine tumours (wdNETs)

Anna Dafnis[1], Haseem Raja[1], Bipasha Chakrabarty[2], Angela Lamarca[2], Richard A Hubner[2], Wasat Mansoor[2], Juan W Valle[2] & Mairead McNamara[2]
[1]University of Manchester, Manchester, UK; [2]The Christie NHS Foundation Trust, Manchester, UK.

Background

Neuroendocrine tumours (NETs) are often associated with SPMs. This study aimed to identify SPMs in patients with non-pulmonary wdNETs.

Methods

Patients seen at The Christie with non-pulmonary wdNETs from 2003–2017 were included. After exclusion of patients with hereditary predispositions, notes were retrospectively reviewed for location, functionality, treatment and temporal relation to diagnosis.

Results

Of 854 patients, 100 (11.7%) had a SPM. Median age at diagnosis of NET: 67 years (range 19–86); 51 females, 66%: grade (G)1, 22%: G2, 12% unknown. Sites of NET in order of prevalence: small bowel [SB](55%), pancreas (22%), unknown (13%), appendix (3%), stomach (3%) and other (4%). Median survival of patients with NET diagnosis was 48.5 months. Regarding first SPM diagnosed, 56 were diagnosed prior, 27 synchronous and 17 metachronous to NET; 85, 13 and 2 patients had one, two and three SPMs, respectively. Breast was the most common site of SPM ($n=20$, 80% curative), followed by colon ($n=18$, 100% curative), skin ($n=13$, 100% curative) and prostate ($n=12$, 100% curative); 15 other sites of SPM recorded. Colorectal and breast cancer were the most common SPM for patients with a SB-NET and pancreatic NET (pNET) diagnosis, respectively. Forty-four NETs were diagnosed incidentally. Of 21 patients with a SPM post-NET diagnosis, 12 had non-functional NETs, 3 functional, 6 unknown.

Conclusion

Non-pulmonary wdNETs are associated with high rates of SPMs. Most SPMs are diagnosed pre-NET, potentially indicating treatment-induced selection of neuroendocrine differentiation clones. A high proportion of NETs are diagnosed incidentally. The association between colorectal cancer and SB-NETs supports previous propositions of colonoscopy use in the work up to NET diagnosis, and association of breast cancer and pNET diagnosis may suggest a possible common pathway alteration in phosphoinositide-3-kinase (PI3K)/protein kinase-B (AkT)/mTOR pathway. Tumourigenic peptides secreted by functional NETs do not appear to have an impact on SPM development within the cohort of patients that develop SPM post-NET.

DOI: 10.1530/endoabs.60.P03

P04

A case series of diffuse idiopathic pulmonary neuroendocrine cell hyperplasia

Grace Pink, Isheunesu Mapfunde & Beatriz Lara
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Diffuse Idiopathic Pulmonary Neuroendocrine Cell Hyperplasia (DIPNECH), which was formally recognised in 1992, has been described as an idiopathic pre-invasive condition that may co-exist with carcinoid tumours. Classically it has been described in women with predominantly obstructive lung function and not in association with smoking. Although many have stable disease, in some documented cases there has been progressive lung

disease leading to the need for lung transplant. There are a few case reports, with the largest including a systematic review identifying 24 cases. We present three further cases of DIPNECH which have been seen by the respiratory and neuroendocrine team, compare these to the previously documented cases and discuss some of the difficulties in diagnosing and managing these patients. Case 1 is a male patient who was noted to have focal vascular invasion and also lymph node involvement with his DIPNECH, this highlights the classification as a pre-invasive lesion. Case 2 is a female who underwent two lung resections for carcinoid nodules on the background of DIPNECH to exclude malignancy. In this case there may have been scope to avoid the second procedure in light of the initial findings. Case 3 is a further female case who was known to have Cushing's disease, after presenting with shortness of breath she had chest imaging which confirmed multiple nodules which were noted on biopsy to be carcinoid tumours. In this case steroid treatment would not have been appropriate to manage her breathlessness and she was instead managed with somatostatin analogues after seeing the neuroendocrine team.

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P05

Problematic bronchial carcinoid

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We present the case of a 26 year old female who presented unusually at the age of 19 with left basal pneumonia. This was deemed to resolve on follow up chest X-ray, however she was given a diagnosis of asthma and used a salbutamol inhaler for wheeze. She re-presented with a left lower lobe pneumonia in 2018, which did not resolve with antibiotics. She was re-admitted a month later and noted to have a left lower lobe collapse. She underwent a bronchoscopy which showed a proximal tumour which was nearly fully occluding her left main bronchus. She underwent an open lobectomy which had to later be converted to a completion pneumonectomy. Histological analysis confirmed a typical carcinoid tumour. This case highlights the importance of early imaging and bronchoscopy for unexpected findings in young patients. She was not seen at the hospital for her worsening respiratory symptoms and had no lung function tests arranged. We present the imaging, endoscopic pictures, and histology of this case.

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P06

Identifying information and support needs for patients with Merkel Cell Carcinoma

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Background
Merkel cell carcinoma (MCC) is a neuroendocrine tumour of the skin. It is a rare, highly aggressive cancer with a high propensity for recurrence and an increasing incidence rate. Feedback from patients and clinicians suggests there is very little accessible MCC specific patient information and support available. To improve patient access to accurate and reliable information and support, the NET Patient Foundation are developing existing services to provide MCC specific information and nurse support.
Aim
To establish MCC patients current sources of support and information and identify gaps in provision and patient preferences.
Method
This was an international survey, data was collected from March 2018 – May 2018. Questionnaires were available online and through MCC clinicians.
Results
Thirty patients responded. Written information: Just over a third of respondents had received written information specifically addressing MCC (36%). CNS support: Two thirds of respondents (67%) didn't have access to, or didn't know, if they had a specialist nurse.
Community support: Only 8 respondents had been signposted to support outside the hospital setting.
Support preferences: Eighteen respondents answered this question. The most popular forms of support were email (15 respondents would or might use), online forum (14 respondents would or might use) and support groups (14 respondents would or might use). Least popular was a cancer centre (11 respondents would or might use).
Travel distance: A quarter of respondents were travelling 25 – 50 miles to hospital appointments.
Discussion
The small number of patients receiving written information and with access to a specialist nurse reflects the need to provide more information and support dedicated to MCC. This supports informal feedback from clinicians who report having nowhere to direct patients to for more information and support outside their consultations. There is a dearth of published evidence about MCC patient's information and support needs. These survey results have been used in conjunction with other sources of anecdotal evidence to develop NET Patient Foundation MCC services including a patient information leaflet (available in print and online) and webpage, with further online support services planned.

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P07

Bone metastases (BMs) in patients with neuroendocrine neoplasms (NENs): Prevalence and clinical management in a tertiary cancer centre

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Background
Bone metastases (BMs) are rare in neuroendocrine neoplasms (NENs). There is no global consensus on the optimal management, and treatment is often extrapolated from experience in other tumour groups. The aim of this study was to review the current management and outcomes of patients with BMs in NENs.
Method
A retrospective study was performed of all patients with NENs, except G3 lung NENs, treated at a tertiary centre from April 2002–March 2018. Baseline characteristics, nature of BMs, treatment received and overall survival were evaluated. Statistical analyses were performed using SPSSv23.0/STATAv12.
Results
A total of 1459 patients were screened; of these 85 (7%) had BMs; median age 58 years (IQR 47.5–67.5). The majority had a gastro-entero-pancreatic primary (49%, $n=42$) followed by lung (25%, $n=21$), unknown primary (20%, $n=17$), and 'others' (6%, $n=5$). Two-thirds ($n=57$) had G1-2 neuroendocrine tumours, and 41% ($n=35$) had functional disease. Twenty-four patients (28%) presented with de novo BMs at first NEN diagnosis, and 47 patients (55%) developed BMs synchronously with other distant metastases. In the remaining 38 patients (45%) in whom BMs were 'late events', median time to development of BMs was 14.0 months (95%-CI 3.1–24.9). BMs were 'widespread' in 61% ($n=52$). Although only 35% ($n=30$) reported symptoms at initial diagnosis of BMs, the majority (78%) later developed symptoms (pain/hypercalcaemia 64%, skeletal-related events 20%). BMs were mainly managed with analgesia (44%, $n=37$). Radiotherapy and bisphosphonates were used in 34% ($n=29$) and 22% ($n=19$), respectively. Surgery was rarely performed (2%, $n=2$). The main reason for not requiring radiotherapy and/or bisphosphonates was that pain was adequately controlled with analgesia and/or systemic treatment. After a median follow-up of 30.9 months and 68% deaths, median overall survival from identification of BMs was 31.0 months (95%-CI 19.6–42.4) and 18.9 months (95%-CI 8.7–29.1) from time of development of BMs-related symptoms.
Conclusion
Most patients with BMs will develop symptoms. Although the majority appear to be adequately managed with analgesia, the utility of radiotherapy and/or bisphosphonates should be prospectively and systematically explored further for its potential impact on patient outcomes (both in terms of survival and quality of life).

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P08

Periodic endoscopic surveillance in patients with low risk type I gastric neuroendocrine tumours (gNETs) also detects associated gastric adenocarcinoma in a subset of patients

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Background
People who have autoimmune atrophic gastritis commonly develop type 1 gNETs, but are also at increased risk of developing gastric adenocarcinoma. Type I gNET patients usually have multiple gastric polyps and have an excellent prognosis when the polyps measure.
Method
Retrospective audit of type I gNET patients managed within Liverpool ENETS Centre of Excellence 2004–2018.
Results
86 patients (median age 67 years, 54 female) had histologically confirmed type I gNETs. Median polyp number was 8 (range 1–50) and median diameter of the largest polyp was 7 mm (range 1–50 mm). 48 patients had grade 1 and 15 grade 2 tumours (information not available on 23 as Ki67 immunohistochemistry was not routinely performed in the earlier years of the audit period). Initial management involved endoscopic resection in five cases and partial/total gastrectomy in nine. Three patients chose no follow up and one died from an unrelated cause soon after diagnosis. 68 patients entered an endoscopic surveillance programme (median follow up 43 months (range 1–162 months), median number of endoscopies 3 (range 1–10)). Two patients showed increases in polyp diameter to 14 mm (no intervention undertaken), two showed increased grade from 1 to 2 (no intervention undertaken as polyps measured 7 mm) and one patient developed an increase in gNET size and grade, but was unfit for intervention due to cirrhosis. One patient developed gastric adenocarcinoma requiring gastrectomy and one developed high grade gastric dysplasia (HGD) requiring endoscopic resection. 61 patients showed no significant change.
Conclusion
5 of 68 patients developed changes in gNET size/grade, but no treatment was undertaken. Two patients developed gastric adenocarcinoma/HGD needing intervention. Although regular endoscopic surveillance detects changes in gNETS in a small proportion of patients, it is also important for the detection of gastric adenocarcinoma.

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P09

Lesson learnt: severe skin reaction to somatostatin analogue injections

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Background
Very little is written regarding injection site reactions to somatostatin analogues and although very rare we are unprepared in dealing with these reactions. Patients are then met with an uncertain clinical team leading to significant delay in treatment. This poster aims to highlight the potential risks of injection site reactions by sharing an extreme case study. It will also share our attempt to deal with injection site reactions, lesson learnt and recommendations for the future. According to the product information pain, swelling and skin reactions are commonly reported by patients receiving somatostatin analogues. 'Small subcutaneous nodules overlying the gluteal muscles' are often reported in Ct scans. However I could only find one other report of such a rare skin reaction that required surgical intervention.
Clinical case
Mrs. A is 74 year old lady with a neuroendocrine tumour of the terminal ilium and Liver metastases. A 4 weekly Somatostatin Analogue was started and given at home by a specially trained nurse. Mrs A complained that her injection sites were painful and said that she felt as if the drug was not dispersing. In total she received 4 injections. After the fouth injection she was reviewed in clinic. She had 3 area's which were clearly breaking down. One area was ulcerated requiring a dressing that the lady had put in place herself. Practice nurses started to dress the wound 3 times a week Consultant oncologist referred Mrs. A to the a surgeon who in turn referred her to plastic surgeons. There were delays in referrals being received. She was finally seen by a plastic surgeon 8 months following the referral from the oncologist. She received surgery a few weeks after this leaving significant scars.
Conclusion
Injection sites in patients receiving subcutaneous long acting somatostatin should receive regular examination for signs of fat necrosis. Patients experiencing continuous pain or discomfort in injection sites should be considered for an alternative formulation of somatostatin. Prompt assessment and escalation to the surgical teams is required to reduce an impact to patient's quality of life.

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P10

Everolimus – associated grade 4 pneumonitis: a case report and literature discussion

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Noninfectious pneumonitis is a recognised toxicity associated with mTOR inhibitors, such as everolimus. We report a 75 year old female with histologically confirmed on colonoscopy, non-functioning Grade 2 (Ki 9%) *in situ* terminal ileal NET with ileocolic lymphadenopathy and multiple liver metastases, who was commencedon somatostatin analogue therapy at presentation in May 2017, but developed progressive disease on CT by February 2018. Based on RADIANT – 4 which showed an improved progression – free survival, therapy was started with everolimus at 50% dose modification (5mg orally) due to the risk of potentiation with concomitant verapamil, a moderate CYP3A4 inhibitor, but which is not considered a contraindication. The patient was admitted 3 weeks after starting treatment, initially with mucositis and diarrhoea: everolimus was stopped, and CXR was clear. Within 5 days, the patient developed fever, dry cough and rapidly progressive, life – threatening dyspnoea requiring HDU outreach support. CTPA showed marked ground glass opacification in all lobes with new pleural effusions. IV antibiotics, including septrin to cover PCP, were commenced, and high dose iv methylprednisolone. The patient improved rapidly and was subsequently discharged home. Repeat CT scan performed 2 months later showed complete resolution of pneumonitis, and, surprisingly after such a short course of therapy, some improvement in liver metastases. In RADIANT-4, noninfectious pneumonitis was reported in 16% of patients, with only 1% being grade 3, and no grade 4 cases; similarly in RADIANT-3, all grades was 16%, but 5 patients (2.5%) had grade 3/4. Interestingly, although experience in NETS is limited, in patients with metastatic renal cell carcinoma where everolimus has been widely used, CT – verified pneumonitis was 34%, and was associated with longer progression – free and overall survival. Whilst the SPC of everolimus advises monitoring for 'clinical symptoms or radiological changes; fatal cases have occurred', we believe that the incidence of noninfectious pneumonitis may be under reported in patients with advanced grade 1/2 NETS, and that serial imaging with CT surveillance rather than CXR, and early recognition of mild or even asymptomatic cases, may prevent life threatening complications.

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P11

Nutritional status of patients at diagnosis with a bronchial NET

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Background
Sarcopenia is characterised by a loss of muscle mass and function and is negatively correlated with quality of life and clinical outcomes. It may be present despite a healthy or even high body mass index (BMI). Up to a quarter of NET patients are at risk of malnutrition, which may impact treatment outcomes and length of hospital stay. Research has shown that patients with pancreatic and intestinal NETs are at higher risk of weight loss than bronchial NETs. With an increased incidence of bronchial NETs, this study aimed to determine the nutritional status of these patients on diagnosis.
Methods
Newly diagnosed patients being seen in a NET outpatient clinic between March 2017 and January 2018 were assessed using an amended Royal Free-Subjective Global Assessment, overseen by a qualified dietitian. Factors impacting nutritional intake and losses were collected. Anthropometric measurements included: weight, height, BMI, hand-grip strength (HGS), mid upper arm circumference, and triceps skin-fold thickness. Mid arm muscle circumference (MAMC) was also calculated.
Results
Thirteen patients (11 female, 2 male, aged 19–77 years) with a new bronchial NET diagnosis consented. On measuring, 2/13 patients had a healthy BMI (20–24.9 kg/m^2), 6/13 were overweight (25–29.9 kg/m^2), 4/13 were obese ($\geq$30 kg/m^2), and 1 was excluded from measuring BMI due to pregnancy. Despite being well nourished according to BMI, 75% of patients whose HGS was measured had a reading below normal for age (9/12 patients; 1 was unable to use the dynamometer). Of those with a BMI $\geq$25 kg/m^2, 3 had a MAMC below 5th percentile. Weight loss was reported in 3/13 patients and 3/13 had low fat stores. A small proportion of patients reported symptoms impacting on nutrition.
Conclusion
Reduced muscle function was observed in the majority of patients with a new bronchial NET diagnosis regardless of BMI and other parameters. Though a small

sample size, this study demonstrated the importance of using functional measures to assess nutrition rather than relying on standard measures which risk missing signs of sarcopenia. It also highlighted the importance of a multidisciplinary approach to NET treatments involving structured diet and exercise advice.

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P12

Glenfield Pulmonary Neuroendocrine Guidelines

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Introduction

Accurate survival data for patients with neuroendocrine tumours (NETs) across the UK has been difficult to capture. Individual centres often report good survival rates, however, national data has not previously been available. Pulmonary neuroendocrine tumours (NETs) cover a spectrum of histological disease, including typical carcinoid, atypical carcinoid and large cell neuroendocrine carcinoma. Surgical resection with curative intent is advocated in the majority of cases provided the patient is fit enough to tolerate lung resection. There is little consensus between key international groups on the most appropriate post-surgical follow up guidelines for pulmonary NETs. Based upon evidence available, existing guidelines and individual clinical experience, we have developed the Glenfield Pulmonary NETs Guidelines which we present for discussion. The majority of NET recurrences occur in the first couple of years, but recurrence may occur at 10 years, or more, after initial resection. Whilst 'longer-term follow up' of these patients is widely recommended there is no consensus on the precise duration of this follow up, nor the frequency of clinical review or repeat imaging/investigations. Our regional guidelines cover initial assessment of each patient and advocate consideration of surgical resection in the majority of cases, even in N2-positive disease (given the normally slow progression of NETs). Most cases will initially be discussed in the local lung cancer multidisciplinary meeting (MDT). However, it is advised that biopsy-proven cases are discussed in the regional, specialist, neuroendocrine MDT. The key considerations with regard to post-surgical follow-up are its duration, as well as repeat imaging modality and frequency. Initial follow up reflects our local lung cancer protocol (3 monthly clinic for 2 years then yearly with repeat CT chest at 6 months, 12 months, 2 years and 5 years) but this annual clinic review is then extended for a total of 20 years follow up. Contrast CT is accepted as the gold-standard imaging and this is recommended every 3 years after the initial 5 year follow up period. In contrast to the European Neuroendocrine tumour society guidelines, repeat octreotide scans and bronchoscopies are not recommended in the majority of cases. Our guidelines involve less frequent imaging than the European groups may advocate, however, we feel these guidelines are appropriate and safe, whilst considering wider factors such as patient preferences and health service funding.

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P13

Automated finger prick genomic diagnosis of neuroendocrine tumors

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Background

The diagnosis of neuroendocrine tumor disease has been tardy due to a lack of sensitive, noninvasive technology to facilitate identification. In the 1960's, diagnosis required tumor tissue attained by surgery or biopsy. Identification was by histopathology and immunohistochemistry (1975). Acquisition of information was limited by the morbidity of invasive strategies, inability to reassess and interpretation was user-dependent with low kappa values. The introduction of molecular strategies (1990–2000) using gene expression assays was comparable to histology with NET detection analogous to accuracy in breast or colon cancer. The limitation remained the requirement of tissue.

Aim

To define molecular genomic signatures for NET in blood by developing automation and micro-assay techniques.

Results

In 2005, we defined transcriptome profiles of gastrointestinal and pancreatic NETs and. In 2010, we developed molecular-based tissue classifiers utilizing machine learning and multigene analyses. Although this strategy was $>95\%$ accurate it still relied on tissue. Between 2010–2015, we investigated if blood was an alternative compartment for NET gene identification and demonstrated that blood transcriptomes and mRNA expression in whole blood (1ml) identified 51 genes that were co-expressed in tissue ($R>0.8$). Scores derived from genes co-expressed in blood and tissue were equivalent and provided the basis for a 'liquid' biopsy (NETest). Metrics were $>90\%$ sensitivity and specificity. Clinical evaluation ($n>5{,}000$ patients) demonstrated the multigene assay to have clinical utility as a prognostic biomarker. In 2017, to facilitate measurement, we then automated the assay using targeted PCR and spotted plate technology with significant concordance ($P<0.0001$) between standard qPCR ($R>0.95$; $n=280$ NETs, $n=125$ controls). To obviate the cold-chain problem, we created an RNA stabilization buffer that maintains NETest signature integrity at room temperature for up to 10 days. Comparison of 120 matched samples show significant concordance in NETest levels ($R>0.93$). Venipuncture, although safer than biopsy, is still a patient-encumbrance. To move beyond venipuncture, we developed a 50ul of blood fingerprick micro-assay system which is concordant ($n=50$) ($R>0.95$) with venipuncture.

Conclusion

We have demonstrated that a NET gene expression assay in blood is accurate and can be automated and miniaturized. The implications for facilitation of diagnosis and point-of-care management warrant investigation.

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P14

Circulating neuroendocrine tumor gene expression is effective in monitoring peptide receptor radionuclide (PRRT) efficacy

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Background

Predicting and monitoring PRRT is based upon NET overexpression of somatostatin receptor (SSR) to deliver targeted isotope therapy. Imaging SSR expression is $\sim 60\%$ accurate as a predictor of efficacy. However, it and other imaging modalities e.g., CT/MRI, have utility for monitoring response. Specific blood NET gene expression (Positive Predictor Quotient- [PPQ]) is accurate in predicting PRRT response (93–97%, Bodei et al. EJNMMI 2018). The utility of NET transcripts (NETest) as an assessment of treatment efficacy requires evaluation. We examined whether the NETest could monitor PRRT therapy.

Methods

We evaluated three independent, prospective 177Lu-PRRT treatment cohorts from Meldola, Rotterdam, and Bad Berka (total: $n=158$, – 2–5 cycles PRRT). Blood was prospectively collected. Baseline evaluation included the NETest (qRT-PCR – multianalyte algorithmic analyses). Blood samples were collected prior to the last PRRT cycle and at follow-up (2–9 months after therapy). Imaging (CT/MRI) were used to evaluate treatment response. Responders included disease stabilization and partial responders. Non-responders exhibited demonstrable disease progression. All blood samples were measured and analyzed in a blinded fashion. Statistics: Non-parametric Mann-Whitney U-test, Kaplan-Meier survival analyses.

Results

PRRT cohort ($n=158$). Median follow-up: 14–16 months. NETest levels pre-PRRT were 58 ± 25. Responders ($n=103$): Prior to PRRT, NETest was 61 ± 23. At the end of therapy cycles, levels were 38 ± 22 ($P<0.0001$). The change represented an average decrease in score of -20%. At follow-up, scores continued to drop (29 ± 15, $P<0.006$ vs end of therapy score). Non-responders ($n=55$): Prior to PRRT, NETest was 54 ± 28. At therapy termination, levels were 62 ± 28 ($P=0.08$). The change was an average increase in score of $+13\%$. In 103 patients, the NETest score decreased or exhibited no change (pre-PRRT to end of therapy) and 53 exhibited an increase. Those with a decrease or no change in NETest demonstrated a mPFS of 23 months. In those with a score increase mPFS was 14 months ($\chi^2=27.2$, $P<0.0001$, Hazard ratio: 0.21).

Conclusion

Alterations in the NETest blood levels are effective in monitoring PRRT efficacy. A decrease in score from pre-therapy to the conclusion of therapy identifies responders. NETest monitoring of PRRT will facilitate disease management.

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P15

NETest liquid biopsy is diagnostic of lung neuroendocrine tumors and identifies progressive disease

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Background
There are no effective blood biomarkers for bronchopulmonary carcinoids (BPC). We examined the utility of a neuroendocrine multigene transcript 'liquid biopsy' (NETest) in bronchopulmonary carcinoids (BPC) for diagnosis and monitoring of disease status.
Aim
To independently validate the utility of the NETest in diagnosis and management of BPC in a prospective multicenter, multinational blinded study.
Material and methods
Study cohorts: (i) bronchopulmonary carcinoids (BPC) ($n=99$); (ii) healthy controls ($n=102$); (iii) idiopathic pulmonary fibrosis (IPF) ($n=50$); (iv) other lung neoplasia ($n=101$): adenocarcinomas (ACC) ($n=41$), squamous cell carcinomas (SCC) ($n=37$), SCLC ($n=16$) and LCNEC ($n=7$). BPC were histologically classified as TC ($n=62$) and AC ($n=37$). Twenty matched tumor tissue-blood pairs (BPC: $n=6$; SCLC: $n=4$; ACC: $n=5$; SCC: $n=5$) were evaluated. BPC disease status was based on imaging and RECIST 1.0 criteria. Diagnostic metrics and disease status correlation was evaluated. Upper limit of normal (NETest) was 20. Data is mean ± S.D.
Results
NETest levels were elevated in 83% BPCs. NETest levels were significantly increased in BPC (45 ± 25) vs controls (9 ± 8, $P<0.0001$; AUROC: 0.96 ± 0.01). The accuracy, sensitivity and specificity were: 92%, 84% and 100%. NETest was elevated in SCLC (42 ± 32) and LCNEC (28 ± 7). Based on imaging and RECIST criteria, 21 were progressive, 58 stable and 20 exhibited no evidence of disease. NETest levels accurately distinguished progressive (61 ± 26) from stable disease (35.5 ± 18, $P<0.0001$). In NED, levels were 13 ± 7. NETest levels were 100% elevated in metastatic disease. This was irrespective of histology (AC: $P<0.02$; TC: $P=0.0006$). Levels were significantly lower in non-endocrine lung cancers, ACC (18 ± 21) and SCC (12 ± 11) and benign disease (18 ± 25) than BPC (45 ± 25) ($P<0.001$). The correlation between paired tumor and blood for BPC was significant (R: 0.83, $P<0.0001$). The correlation for SCLC (R: 0.68) was significant but not for SCC and ACC (R: 0.25–0.31).
Conclusions
Elevated NETest levels are diagnostic of lung neuroendocrine neoplasia. Blood NETest levels correlate with tumor tissue levels. The levels accurately identify clinical progression as determined by imaging and RECIST criteria. NETest liquid biopsy is an effective diagnostic and has clinical utility in the identification of disease preogression.

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P16

Validation of the NETest liquid biopsy as a diagnostic for gastro-enteropancreatic neuroendocrine tumors (GEP-NETs)

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Background
The NETest, a neuroendocrine multigene transcript 'liquid biopsy', is a novel biomarker for GEP-NETs. Current biomarkers are monoanalyte amines or peptides whereas the NETest is a multianalyte signature providing molecular biological information pertinent to clinical disease.
Aim
Independently validate the utility of the NETest for the diagnosis of GEP-NETs and identification of disease progression.
Material and methods
Cohorts: controls ($n=63$), histologically confirmed NETs ($n=113$), pancreatic [PNET]: $n=68$; small bowel [SINET]: $n=45$). Disease extent at blood draw: CT ($n=110$) or ^{68}Ga-DOTA-TATE PET/CT ($n=72$). Image-positive disease was defined as CT or ^{68}Ga-PET-positive. Both CT/^{68}Ga-PET-negative was considered no evidence of disease (NED). Disease status evaluation was RECIST 1.1-based. NETest assay metrics and disease status were evaluated in image positive disease compared to NED. NETest upper limit of normal: 20. Data is mean ± S.D.
Results
Diagnosis: Image-positive disease was present in 102 (PNET: $n=60$; SINET: $n=42$) and NED in 11 (PNET: $n=8$; SINET: $n=3$). NETest levels were significantly increased (27 ± 23) in all GEP-NETs ($n=113$), vs controls (8 ± 4, $P<0.0001$). In image-positive disease, NETest levels were 36 ± 22 and in NED significantly lower (7 ± 5, $P<0.0001$). NETest elevations in image-positive PNET (41 ± 25) and SINETs (38 ± 23) were comparable. NETest diagnostic metrics: accuracy (94%), sensitivity (99%), specificity (90%). Concordance with imaging: NETest was 92% concordant with CT and 96% concordant with ^{68}Ga-PET. In CT-positive ($n=68$), NETest was elevated in 99% (35 ± 20). In CT-negative ($n=42$), NETest was normal (14 ± 20) in 83%. In ^{68}Ga-PET-positive ($n=58$), the NETest was elevated (38 ± 24) in 98%. In ^{68}Ga-PET-negative ($n=14$), the NETest was negative in 86% (11 ± 11). There were 11 image-discordant results. There were nine ^{68}Ga-PET + ve/CT-ve with NETest positive in 89% and two ^{68}Ga-PET-ve/CT + ve with NETest positive. Disease status: Eighteen patients exhibited progressive disease (PD). PD NETest levels were significantly ($P<0.003$) higher (56 ± 29) than stable disease (30 ± 15).
Conclusions
A positive NETest is an effective diagnostic (>90%) for pancreatic and small bowel NETs. Elevated NETest levels are as effective as imaging in diagnosis. NETest levels accurately identified progression. The NETest may have clinical utility in management of PNET and SINETs.

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P17

Use of choline PET-CT in the diagnosis of neuroendocrine tumours

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Introduction
Choline PET-CT is a recognised modality for imaging prostate cancer; both for initial staging and restaging. It is, however, a non specific tracer and is also positive in numerous other conditions such as inflammatory processes and other malignancies.
Method
We present a case of a 60 year old patient with a PSA of 9 ng/ml and a firm abnormal right prostate lobe. Prostate MRI demonstrated a lesion in the apex of the prostate but no associated lymphadenopathy. The isotope bone scan was negative. As the patient was considered high risk for malignancy and in view of his rising PSA, an 18F choline PET-CT was performed to exclude nodal and distant metastatic disease.
Results
The choline PET-CT scan showed increased uptake at the apex of the right prostate gland corresponding to the tumour identified on pelvic MRI. In addition, there was increased uptake in a conglomerate mass of mesenteric lymph nodes to the right of the midline at the level of L_3/L_4. There was associated calcification and mesenteric stranding. Further foci of relatively reduced uptake were also seen in the liver. A subsequent contrast enhanced CT confirmed the enhancing mesenteric mass lesion and the hepatic lesions in segment VIII. These lesions also demonstrated increased uptake on an Indium Octreotide SPECT CT imaging. This lesion was confirmed to represent well differentiated NET and the patient was commenced on lanreotide treatment.
Discussion
Malignancies including prostate cancer express choline transport and choline kinase enzymes. Choline PET-CT is useful for the staging prostate cancer when conventional imaging is inconclusive/ equivocal or there is undiagnosed spread in high risk cases. It has a sensitivity of 66–81% and specificity 43–87% in prostate cancer. However, as demonstrated it can also be positive in other malignancies including NET and other inflammatory conditions.
Conclusion
Choline PET-CT is not used as a primary diagnostic or staging procedure for NET but it can be diagnosed incidentally on such studies. The CT appearance and location of NET are well recognised with subsequent somatostatin receptor imaging, biopsy and biochemical markers confirming the diagnosis.

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P18

The impact of ^{68}Ga-based PET-CT scanning on the management of patients with sporadic pancreatic neuroendocrine tumours (pNETs)

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Background
Pancreatic neuroendocrine tumours (panNETs) are rare tumours (prevalence 4/100,000). Diagnosis and staging of panNETs requires biochemical screening, cross-sectional imaging (with CT/MRI), endoscopic ultrasound (EUS) and where available, functional imaging using ^{68}Ga-labelled synthetic octreotide analogues using PET-CT due to its reported higher sensitivity and specificity.
Methods
A retrospective, electronic case note study was carried out across three ENETS Centres (Liverpool, Aintree, Royal Liverpool; The Christie, Manchester; and King's College Hospital, London) to investigate the effect of ^{68}Ga-based PET-CT imaging on patient management, in patients with a clinically-suspected or histologically-confirmed sporadic panNET. Patients who had undergone a ^{68}Ga-based PET-CT scan for a panNET were identified using a prospectively populated list.
Results
A total of 172 patients were identified between 2014 and 2018; 52% male, 48% female; with a median age of 68 years (range 13–89). Of these 90% ($n=153$) were still alive (17 (10%) had died; 2(1%) missing data); 83% ($n=132$) had non-functional tumours (based on their biochemical profile) and 17% ($n=27$) had functional tumours (8%, 13 missing data). A confirmed histological diagnosis (from either biopsy/surgical resection) was available in 91% of patients ($n=156$) with imaging only in the remainder. Of patients with histology available 51% ($n=73$) were Grade (G)1 tumours, 46% ($n=66$) were G2 and 3% ($n=5$) were G3; 55% ($n=93$) had localised disease; 18% ($n=31$) were locally advanced and 27% ($n=46$) were metastatic. Indications for performing a ^{68}Ga-PET-CT included diagnosis and staging 36% ($n=62$), consideration for peptide receptor radionuclide therapy (PRRT) 9% ($n=15$) and post-operative assessment or clinical surveillance to look for disease recurrence 55% ($n=93$). In 54% of cases ($n=75$) the evidence provided by the gallium scan was confirmatory and consistent with other imaging findings, in 12% ($n=17$) it resulted in a change of treatment and in 28% ($n=39$) new sites of disease were identified not evident with other imaging techniques. Overall it was deemed to result in a change in management in 39% of cases.
Conclusion
^{68}Ga-based PET-CT imaging in patients with panNETs changes clinical management in 39% of cases by providing supplementary information informing the diagnosis, staging, most appropriate treatment modality and subsequent monitoring of recurrence.

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P19

Imaging in paragangliomas and phaeochromocytomas: a pictorial review

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Imaging in paragangliomas can be challenging as they arise from a number of locations including the adrenals, abdomen, pelvic and thoracic sites of chromaffin sympathetic tissue. They can also arise in the head and neck at sites of parasympathetic tissue. They are considered within the group of heterogenous neuroendocrine tumours. In addition to manifesting at multiple sites, they can metastasise, have variable expression of catecholamines and can be a manifestation of hereditary genetic mutations. They are imaged using a variety of functional imaging techniques that target a number of receptors or pathways. Biochemical markers including metanephrines and noradrenalin can be useful. Functional/nuclear imaging include imaging of catecholamine production (MIBG) (usually used as the first line test of choice), somatostatin receptor imaging (octreotide and 68Ga Dotatate) and glucose metabolism (18F-FDG). MR imaging can also be used, particularly in younger patients in order to limit the exposure to radiation. Upto 30% of paragangliomas can be hereditary and can arise either in the adrenals (phaeochromocytomas) or are extra-adrenal in location. Hereditary paragangliomas and sporadic phaeochromocytomas can be the result of germline mutations in succinate dehydrogenase complex subunits B (SDHB) and are also associated with clinical syndromes including Von Hippel Lindau, MEN and NF1. This group of patients can presents with paragangliomas at a young age. Lesions canalso be multiple, bilateral and are often extra-adrenal. This is complicated when (particularly in hereditary cases) patients are asymptomatic or have a neligible elevation of their biochemical markers such as noradrenalin or metanephrines. We discuss the optimal use of multimodality imaging in paragangliomas and phaeochromocytomas including functional imaging, MRI, ultrasound and CT.

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P20

Chest metastases in advanced small bowel neuroendocrine neoplasms: incidence and outcome

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Introduction
Liver is the most common site in patients with advanced small bowel neuroendocrine neoplasms (SBNEN) and distant metastases. On the contrary, lung metastases are relatively uncommon, occurring in 5–13.6% of patients. Although hepatic metastases often progress and have implications to the disease outcome, not enough data are available for lung metastases.
Aim
Our aim was to assess the incidence of chest (including lung, mediastina/hilar lymph node and pleural) soft-tissue metastases, and the outcome of lung metastases, in a series of advanced SBNEN.
Methods
A series of 236 advanced SBNEN was retrospectively reviewed. The presence of chest soft tissue metastases was confirmed by their avidity in Somatostatin Receptor Imaging. The study period was 3 years. No biopsy was performed in any of those lesions.
Results
Thirty four (34/236, 14.4%) had soft-tissue chest metastases. Seven patients (7/236, 2.9%) had lung parenchymal metastases, 23/236 (9.7%) had mediastinal/hilar lymph node (MHLN) metastases, whilst 4/236 (1.6%) had pleural deposits. Three of the patients with lung metastases had also MHLN metastases and one had also pleural metastases. Hepatic metastases were also present in 5/7 (71%) of patients with lung metastases and in 5/23 (21.7%) in patients with MHLN metastases. The mean size of lung metastases was 1.9 cm. In 28/34 (82%), the primary tumours' grade (G) was G1. None of the patients had any symptoms associated with those lesions. Two of the patients (28%) with lung metastases had disease progression, based on size, and at the same time progression of hepatic metastases. Peptide Receptor Radionuclide Treatment (PRRT) was administered, resulting in disease stabilization. PRRT was given to another patient with progressive disease in the liver only, which resulted in partial response in her liver and lung metastatic lesions.
Conclusions
Mediastinal/hilar LN metastases seem to be the most common site of chest soft-tissue metastases in advanced SBNEN, whilst lung parenchymal metastases are quite rare and usually co-exist with hepatic metastatic disease. Lung metastases progress rather uncommonly and almost always when progression of hepatic metastases is also noted. Larger series of patients with longer follow-up are needed.

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P21

Utility of PRRT therapy in invasive intra-cardiac paraganglioma

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We present the case of a 51-year-old woman who attends the NET service at the Oxford University Hospitals Trust with multiple known secretory paragangliomas (predominantly 3-methoxythyramine), including a carotid body tumour and, most recently, an intrapericardial paraganglioma. She is *SDHC* mutation positive. Multiple surgical resections of paragangliomas, at sites other than the cardiac lesion, had previously been undertaken. Due to disease progression and symptomatic burden, surgical resection of the intrapericardial paraganglioma was attempted in 2016. Unfortunately, on direct visualisation the tumour was found to be invading the left and right ventricular myocardium, and was supplied by the right coronary artery, which was coursing through the tumour. As such, the tumour was deemed inoperable and the procedure was abandoned. Due to the significant burden of symptoms, and the potential for catastrophic haemorrhage due to disease progression, peptide receptor radionuclide therapy (PRRT) was considered. All tumour sites were shown to be DOTATATE avid on Ga-PET CT. It was hoped that PRRT would halt disease progression and thus reduce the long-term risk of haemorrhage. After thorough discussion of the potential risks and benefits the patients elected for PRRT. Two cycles of Yttrium-90 DOTATATE were administered in July 2017 and November 2017 respectively. Since completing PRRT the patient has reported an improvement in exercise tolerance, though oxygen requirements, and other objective parameters, remain unchanged. Follow-up imaging demonstrated an interval reduction in the size of the carotid body tumour and stability of the intrapericardial tumour.

Conclusion

The decision to treat with PRRT in this case hinged on the assumption that dramatic tumour shrinkage, with resultant catastrophic haemorrhage, was unlikely. Fortunately this has proved to be the case and the patient appears to have enjoyed some symptomatic benefit from treatment. The future risk of catastrophic haemorrhage due to disease progression is unclear, but interval stability of the intrapericardial tumour on post treatment imaging is encouraging. This case illustrates that PRRT treatment is likely safe in the setting of pericardial disease, may help to slow disease progression and is a viable therapeutic option in similarly challenging cases where an applicable evidence base may is a viable therapeutic option in similarly challenging cases where an applicable evidence base may be lacking.

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P22

Diagnostic features and management options for duodenal neuroendocrine neoplasms: results from a multi-centre series

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Background

Duodenal neuroendocrine neoplasms (dNENS) have an incidence of 0.19 per 100,000 according to SEER data from 2007. This figure is on the rise, resulting from increased number of upper gastrointestinal endoscopies and CT scans performed, and greater awareness of NENs. A larger proportion are found incidentally and are non-functioning. There is great heterogeneity in the behavior and management of dNENs, many are diagnosed at a far earlier stage, without the presence of metastatic disease, it is unclear which factors affect their natural history.

Aim

To analyse factors that can affect the behaviour and management of duodenal NENs.

Methods

Using a pre-developed clinical research form (CRF), we retrospectively analysed clinico-pathological data of patients with histologically proven dNENs from three ENETS Centres of Excellence. Ampullary NENs were ex from our study.

Results

102 patients were identified. Median age at diagnosis was 63 (range 32–87). Sub-classification, found two poorly differentiated neuroendocrine carcinoma's, three carcinoids, nine gastrinomas, one paraganglioma and 83 non-functioning dNENS. Size of primary was determined in 97 patients; <5 mm $=30$, 6–10 mm $=19$, 11–20 mm $=25$, >2 cm $=20$. Over 80% were located in D1. Lymph node metastases were seen in 35% patients, and liver metastases were seen in 22% patients. Significant factors associated with metastases were size and grade and functional tumours. Endoscopic resection was performed in 17 patients, with R1 resection rate approaching 50%. Surgery was performed in 31 patents, 18 patients had unresectable disease at presentation and 36 were placed on active surveillance.

Conclusions

Duodenal NENs demonstrate significant heterogeneity in their behavior and the subsequent development of metastatic disease. Identifying the key predictors of behavior will allow tailoring management for each patient and avoiding unnecessary surgery or endoscopic intervention in those with low malignant potential. The relative high R1 resection rate at endoscopy of dNENS suggests that further studies are required to determine which patients are suitable for this and to evaluate newer techniques. Greater numbers are required to gain statistically significant findings from this analysis and we encourage other NET centres to take part in this study in the future.

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P23

Seeking the unseen: a case of occult sporadic insulinoma: localization, surgical strategy: a rare case

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Insulinoma is a rare pancreatic neuro endocrine tumour. It is the commonest cause for endogenous hyperinsulinaemic hypoglycemia in a seemingly well individual. Insulinomas are small tumors which may not be detected on conventional imaging modalities. Image negative endogenous hyperinsulinemia poses a diagnostic challenge to the clinicians. Interventional radiological techniques with higher sensitivity can be used in such situations for correct localization of the small s for better accuracy and for planning of successful surgical resection. A 39-year-old male presented with established Whipple's triad for past 10 months. Clinical evaluation did not reveal possible underlying critical illness, organ failure, autoimmunity, hormone deficiency or surreptitious/malicious hypoglycemic drug use. Biochemical testing including C-peptide level and serum insulin level during hypoglycemia on supervised 72-hour fast test concluded endogenous hyper-insulinaemia as the underlying etiology. Localization testing with MRI and CT abdomen were unable to localize a tumor. Selective arterial calcium stimulation test localized a lesion in distal pancreas which was confirmed by intraoperative ultrasonography. Insulinoma was proven on histological examination following complete enucleation, supported by immunohistochemistry profile with WHO grade 1 tumor. Patient recovered without complications and at 1 year follow up, he was asymptomatic.

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P24

Assessment of fat-soluble vitamins and trace elements in neuroendocrine tumour (NET) patients on somatostatin analogues

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Introduction

NETs are a diverse group of neoplasms that originate from cells of the diffuse endocrine system. Often somatostatin analogues (SSA) are used as a first line treatment. Loose stools and steatorrhea are common adverse effects of SSA. This can affect the absorption of fat soluble vitamins and trace elements (TE). In this study we assess the prevalence of these deficiencies.

Methods

A prospective study of 66 patients on SSA. Vitamins A,D,E,K and the trace elements; copper, zinc and selenium were analysed. Duration of SSA use, stool type, treatment with creon and vitamin supplements were also recorded.

Results
Mean age was 64 +/− 10 years. 97% (64) of primary tumour were small intestinal NET, 1.5% (1) pancreatic NET and 1.5% (1) hindgut NET. 47% of patients were deficient in at least one vitamin and 55% in at least one TE. 8.6%, 19%, 5% and 47% deficiencies were seen for vitamins A,D,E and K. It was 4.7%, 51.6%, and 16% for copper, zinc and selenium. Two patients had deficiencies in all fat soluble vitamins and TE. 53% (35) of patients reported taking multivitamins, vitamin D or a combination of both. They continued at the same dose during follow up. 20 patients (31%) recorded loose stools, of these, 70% were on creon pancreatic enzyme therapy. 42% (28) of patients were on Octreotide; 24 (86%) were on Octreotide LAR 30 mg, 1 (3.5%) on 40 mg and 1 (3.5%) on 50 mg, 2 (7%) were on SC Octreotide >600 mcg daily. 58% (38) of patients were on Lanreotide autogel; 95% (36) were on 120 mg and 5% (2) on 90 mg. Mean duration of SSA use was 6.3 +/− 4.1 years. 94% of patients have been on SSA for over a year.
Conclusions
Deficiencies in fat soluble vitamins and TE is not uncommon in NET patients on SSA. Creon use, prescribed for NET patients with diarrhoea and steatorrhoea was more frequent in patients on SSA for more than a year. Supplementation of fat soluble vitamins and TE should be considered.

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P25

Deficiencies in fat soluble vitamins and TE is not uncommon in NET patients on SSA. Creon use, prescribed for NET patients with diarrhoea and steatorrhoea was more frequent in patients on SSA for more than a year. Supplementation of fat soluble vitamins and TE should be considered

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Introduction and Aims
Neuroendocrine tumours (NETs) are rare, slow growing tumours originating from cells of the neuroendocrine system. Although often indolent and asymptomatic, a significant proportion turn out to be malignant and tough to manage. Over the last few decades, the incidence of NETs has increased more than 6-fold, likely owing to improved detection of early stage disease. Age-adjusted annual incidence of NETs currently stands at 6.98 per 100000. As such, there has been an increased demand for imaging such tumours. We review our 10-year experience of NET imaging using octreotide and metaiodobenzylguanidine (MIBG). The latest advance in somatostatin receptor-based imaging is the use of 68 Gallium-labelled radioligands. Thus, we highlight our experience and hurdles of establishing a 68Gallium PET-CT service at our centre.
Methods
This retrospective study looks at the nuclear medicine database between 2008-2018, observing the number of octreotide and MIBG scans performed per annum.
Results
Between 2008–2018, a total of 415 octreotide and 130 MIBG scans were performed. Demand for MIBG imaging showed a variable year-on-year demand, whilst octreotide receptor imaging showed a stable demand from 2008 to 2013 followed by an upward trend from 2014. There has been a 90% increase since 2014.
Conclusion
On the whole, our centre has demonstrated a rise in the demand for NET imaging, which concurs with literature reports of increased incidence of NETs over the last few decades. Due to this and following updates to guidelines, we are looking to implement a 68Gallium PET-CT neuroendocrine imaging service due to its higher sensitivity, accuracy and potential for greater patient throughput.

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P26

Tumour growth rate (TGR) in neuroendocrine tumours (NETs): changes following systemic treatment and external validation of previous findings; the GREPONET-2 study

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Background
TGR represents the percentage change in tumour volume per month (%/m). Previous results from the GREPONET study (A. Lamarca *et al*, ENETS 2018) showed that TGR measured after 3 months (TGR3m) of starting systemic treatment (ST) or watch and wait (WW) was an early biomarker predicting progression-free survival (PFS) in NETs.
Methods
Pts from 7 centres with advanced grade (G) 1/2 NETs from the pancreas (P)/small bowel (SB) initiating ST/WW were eligible. Scans performed at pre-baseline, baseline and 3(+/−1) months of study entry were retrospectively reviewed for calculation of TGR at baseline (TGR0) and TGR3m. Study objectives included: Aim-1: explore treatment-induced changes in TGR (TGR3m-TGR0) (paired T-test) and Aim-2: validate TGR3m (<0.8%/m vs ≥0.8%/m) as an early biomarker in an independent cohort (Kaplan-Meier/Cox Regression).
Results
Out of 785 pts screened, 127 were eligible. Patient characteristics: 59.1% P, 40.9% SB; 62.9% G2; 72.4% ST-naïve. ST: somatostatin analogues 37.8%, chemotherapy 32.3%, targeted therapies 18.1%, PRRT 3.9%; WW 7.9%. Mean (SD) TGR0 and TGR3m were 5.4 (14.9) and −1.4 (11.8), respectively. Mean (SD) paired-difference between TGR3m-TGR0m was −6.8 (19.3) ($P<0.001$). Subgroup analysis by type of ST showed most marked TGR-changes (mean (SD); P) with targeted therapies (−11.3 (4.7); 0.0237) and chemotherapy (−7.9 (3.4); 0.0261). Median PFS for patients eligible for Aim-2 ($n=97$) was 16.2 m (95%CI 11.7–18.6); median follow-up 22.9 m. TGR3m cut-off of 0.8%/m stratified pts in two groups with different outcomes: the pts with TGR3m≥0.8 (31 pts; 31.9%) had a significantly shorter median PFS (12.2 m (95%CI 5.6–16.2)) vs. TGR3m<0.8 (66 pts; 68.1%; median PFS 18.6 m (95%CI 10.8–20.9)); Cox univariate P 0.011. Both TGR3m and tumour grade were significant in univariate Cox regression and included in multivariable Cox regression: TGR3m≥0.8 (vs.<0.8) (HR 2.55 [95%CI 1.64–3.97]; $P<0.001$), grade 2 (vs.1) (HR 2.02 (95%CI 1.25–3.27); P 0.004).
Conclusion
TGR varies significantly after treatment initiation, thus suggesting its role as biomarker for monitoring response to therapy. The role of high TGR3m as a factor associated with shorter PFS was validated in this independent cohort and maintained its robustness as an early radiological biomarker.

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P27

Unmasking ectopic ACTH secretion and changing functionality of a pulmonary neuroendocrine tumour with carcinoid syndrome

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Pulmonary neuroendocrine tumors (NET) are well recognized, but quite an uncommon group of disorders to cause ectopic Cushing's syndrome. Pulmonary NETs have also undergone a change in treatment paradigms. We present a 62 year old female with incidentally detected left lower lobe lung nodule with biopsy proven well differentiated NET with ki67 index of 5–10% in 2011. She had a metachronous slow growing left sided renal tumor (hypernephroma), long

standing type 2 diabetes, hypertension, episodic dry flushing and chronic diarrhoea. Clinical examination was normal apart from morbid obesity with a BMI of 40. Whole body FDG -PET CT showed intense FDG uptake within the left lower lobe of lung which involved the pericardium without uptake in lymph nodes or in renal lesion. Both Chromogranin A (29.9 nmol/L) and 24 hr Urine 5HIAA (40 mmol/L) were elevated, thus diagnosis of carcinoid syndrome was made and she received Octreotide LAR 30 mg monthly, with clinical and biochemical resolution. Subsequent imaging showed stable lung lesion and her echocardiograms were normal. Whilst undergoing long term surveillance, 6 years on, she had 2 episodes of bowel ischemia requiring extensive bowel resection resulting in prolonged hospital stay, during which she was off somatostatin analogue therapy for 7 months. In this period, she developed clinical features of Cushing's syndrome, which prompted biochemical re-evaluation. She failed to suppress on overnight dexamethasone suppression test with the resulting cortisol level being 280 nmo/L (normal response to suppress $<$ 50 nmol/L) with elevated 24 hour urine free cortisol (201 nmo/L and 115 nmol/L over 24 hours) and ACTH of 90.4 ng/L suggestive of ACTH dependent Cushing 's syndrome. Corticotroph Releasing Hormone (CRH) Test suggested diagnosis of ectopic ACTH secretion. The diagnosis of ectopic Cushing's syndrome secondary to pulmonary neuroendocrine tumor was made and she was restarted on Octreotide LAR. Within two months of therapy, she demonstrated remarkable clinical and biochemical improvement. This case illustrates the unmasking of ectopic ACTH secretion and changing functionality of a pulmonary neuroendocrine tumor. It is a reminder of the prolonged surveillance and vigilance needed the management of neuroendocrine tumors.

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P28

Bronchial carcinoid presenting in young adults. A case series highlighting issues in disease management, unusual sites of metastases and long term surveillance

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The prevalence of bronchial carcinoid, both typical (TC) and atypical (AC), has increased significantly over the past 30 years, most likely as a consequence of better awareness and diagnostic tools e.g. carcinoid specific immunohistochemistry stains. The peak incidence of TC and AC are in the fourth and fifth decades of life respectively. Diagnosis at younger ages is much rarer although carcinoid represents one of the commonest pulmonary tumours in children, teenagers and young adults. We present 3 cases of bronchial carcinoid tumours arising in patients in their teens or 20's, particularly highlighting management issues either related to their young age or unusual pattern of metastases. Case 1: An 18 year old woman presenting with chest pain. Central lung mass detected on CT and biopsy reveals typical carcinoid. Surgical resection - middle and lower lobectomy. 12 months later - enlarging sub-carinal lymph nodes. Case 2: A 20 year old woman presents with cough and reduced exercise tolerance. Left bronchial tumour detected. Left upper lobectomy and sleeve resection for typical carcinoid. 2 years later development of axillary and sub-cutaneous nodules - recurrent disease. Case 3: A 28 year old woman presents with Cushing's syndrome. Ectopic ACTH secretion diagnosed. Two sub-cm lung nodules, with no uptake on octreotide or Ga68 PET scan, detected. Wedge resection reveals typical bronchial carcinoid. Further symptoms of Cushing's after 10 months - relapsed disease in lung and mediastinum. A concise review of each case, including relevant images, and their on-going care will be used to draw attention to management dilemmas.

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P29

The role of imaging in neuroendocrine tumours

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The imaging of neuroendocrine tumours (NET) is multimodal and is often initiated by cross sectional imaging, usually CT. Imaging with CT demonstrates metastatic disease more frequently than locating the primary lesion. Subsequent imaging relies on somatostatin receptor (SSR) scintigraphy, usually with the use of indium octreotide. SSR scintigraphy is commonly supplemented with SPECT CT to help localise the sites of metastatic deposits more accurately by delineating the associated anatomical structures and often helps to localise the site of primary disease. This approach not only improves diagnostic confidence but also functions to further inform management options. More recently, PET-CT using gallium labelled tracers have proved to be more sensitive in imaging NET; improving on spatial resolution, tumour contrast and speed of acquisition. It has also been used in the direction of neuroendocrine therapy, in particular peptide receptor radionuclide therapy and has been also considered as a replacement for scintigraphy entirely in some centres. We outline the value of imaging including ultrasound, functional and hybrid imaging in the diagnosis and follow up of NET. We will also discuss the value that SPECT CT imaging has over cross sectional and conventional planar SSR imaging. In addition, the added benefit and appropriate use of PET CT and new tracers is also highlighted.

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P30

The impact of ^{68}Ga-based PET-CT scanning on the management of patients with familial pancreatic neuroendocrine tumours (panNETs)

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Background
Pancreatic neuroendocrine tumours (panNETs) may arise as part of an underlying genetic condition such as multiple endocrine neoplasia type 1 (MEN type 1). The value of functional imaging using ^{68}Ga-labelled synthetic octreotide analogues using PET-CT has not been extensively evaluated in patients with MEN1 to determine its value.
Methods
We investigated the effect of ^{68}Ga-based PET-CT imaging on patient management in patients with a clinically suspected or histologically confirmed familial panNET. A retrospective electronic case note study was carried out in three ENETS Centres (Aintree/Royal Liverpool, Christie Hospital, Manchester and King's College Hospital, London). Patients who had undergone a ^{68}Ga based PET-CT scan for a panNET were identified using a prospectively populated list.
Results
We collected data for 52 patients (25 male, 27 female) with mean (SD) age of 50 (17) years; MEN type 1 was the predominant syndrome in 87% ($n=45$). 94% ($n=48$) were still alive and 6% ($n=3$) dead (1 missing). 42% ($n=21$) were non-functional tumours *versus* 58% ($n=29$) with functional tumours. A confirmed histological diagnosis (from biopsy/surgical resection) was available in 86% of patients ($n=44$) with imaging in the remainder. Tumours were in the head/neck, body, tail or were multi-focal in 38, 6, 28 and 28% of cases. Of those with histological grade available ($n=32$): 53% were Grade 1 tumours ($n=17$), 44% ($n=14$) were Grade 2 tand 3% (1) were Grade 3. 68% ($n=34$) were localised, 18% ($n=9$) were locally advanced and 14% ($n=7$) were metastatic. The indications for Ga^{68} PET-CT scans were diagnosis/staging 50% ($n=26$), post-operative assessment/clinical surveillance 46% ($n=24$) and consideration for peptide receptor radionuclide therapy (PRRT) 4% ($n=2$). In 75% of cases ($n=39$) tracer avid uptake was seen with no uptake in 25% ($n=13$). In 48% of cases the scan confirmed information gained from other imaging modalities but in 33% of cases it identified new sites of disease and in 4% ruled out suspected disease with previous imaging. Overall, Ga^{68} based PET-CT imaging led to change in management in 40% ($n=21$) of cases.
Conclusion
^{68}Ga-based imaging in patients with familial panNETs provides supplementary clinical information that guides diagnosis, staging, and most appropriate treatment.

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Author Index