15th Annual Meeting of the UK and Ireland Neuroendocrine Tumour Society 2017
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Diagnostic, monitoring and prognostic challenges in NETs
NETS1
The role of biomarkers in the management of neuroendocrine tumours
Dalinder Singh Mandair
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Neuroendocrine tumours are a heterogeneous group of tumours that arise in diverse anatomical locations and vary greatly in behavior and response to treatment. A biomarker is a characteristic that can be objectively measured and evaluated as an indicator of a pathogenic process or response to treatment. Biomarkers can be diagnostic, prognostic, predictive or surrogate markers of clinical endpoints. The management of neuroendocrine tumours has changed dramatically with the introduction of new therapies with strong evidence of their efficacy from international clinical trials. However there remains significant heterogeneity in treatment response that cannot be predicted by clinical parameters and currently available biomarkers are limited as predictive and prognostic tools and only Chromogranin A is currently recommended by the European Neuroendocrine Tumour Society (ENETS) for monitoring for progressive disease in non-functional NETs. There is a pressing need for biomarkers that help identify more aggressive disease, guide treatment and can be used in surveillance to detect early recurrence or tumour progression. In this talk I will review the currently available circulating biomarkers, both their indications for use and their limitations in clinical practice. There has been great interest in the emergence of novel biomarkers such as circulating tumour cells, NETest and microRNA. I will evaluate each of these biomarkers by presenting the current evidence for their use and discuss their potential applications in real clinical cases.
DOI: 10.1530/endoabs.52.NETS1

NETS2
The role of pathology and the new WHO classification
Adam Christian
University Hospital of Wales, Cardiff, UK.

Neuroendocrine tumours have a number of different classification and staging systems. I will present the latest of these, which include the latest WHO system with the implications for new entities and how they are diagnosed pathologically and any difficulties that arise from this. There will also be a more general discussion about areas that are difficult for the pathologist and where we can add value to the MDT discussion.
DOI: 10.1530/endoabs.52.NETS2

NETS3
Abstract unavailable.

NETS4
Role of Multimodality Imaging
Amy Eccles
Guy’s and St. Thomas’ Hospital, London, UK.

This talk aims to highlight the different tracers that are commonly used in the multimodality imaging of neuroendocrine tumours. It will look at both SPECT and PET tracers and their role in diagnosis, planning treatments and monitoring therapies using case examples.
DOI: 10.1530/endoabs.52.NETS4

Management dilemmas in NETs
NETS5
Neo-adjuvant and adjuvant treatment in bronchial NETs
Wasat Mansoor
Christie NHS Foundation Trust, Manchester, UK.

Collectively, typical and atypical lung carcinoids are referred to as the well differentiated lung neuroendocrine cancers (pulmonary NETS). Pulmonary NETS account for only 2% of all lung malignancies, however, account for 25% of the total NET presentations. The incidence and prevalence of these cancers is growing. Most pulmonary NETs tend to be localised at presentation and, therefore, amenable to surgical resection. Following surgical resection, there is very little evidence based guidance on how these patients should be followed up, what the risk factors for relapse are or whether there is a role for the administration of adjuvant therapy. Published guidelines are at odds with each other regarding this issue. It is clear that some cohorts of resected patients do relapse and may benefit from adjuvant treatment. However, currently these cohorts remain ill-defined. Furthermore, due to a historic scarcity of evidence, it is currently not clear what type of therapy should be used as adjuvant treatment. In recent years, better therapies with more robust evidence have emerged. Our basic understanding of pulmonary NETs is also improving. These factors in combination with an increasing incidence/ prevalence of the disease are bringing the question about adjuvant therapy back into sharp focus.
DOI: 10.1530/endoabs.52.NETS5

NETS6
Type I gastric NETs: Surveillance, Endoscopic Resection or Surgery
Raj Srirajaskanthan
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There are three distinct types of gastric Neuroendocrine tumours using the ENETS classification system. Type 1 gastric NETs are most common, accounting for 55–70% of all gastric NETs. Epidemiology studies have suggested an increasing incidence of gastric NETs. Generally type 1 gastric NETs are multifocal in nature and arise in a background of chronic atrophic gastritis. Type 1 Gastric NETs arise from histamine secreting ECL cells, hypergastrinaemia due to excess gastrin release, for example unopposed gastrin secretion occurs in achlorhydria in patients with atrophic gastritis. Management is generally endoscopic surveillance annually to ensure no development of a dominant lesion. The risk of lymph node or distant metastasis is low 1–5% reported in different series. This risk of metastatic spread is linked to size of lesions. Therefore, the recommendation is for lesions over 10 mm to be removed endoscopically if feasible. This can be performed via endoscopic mucosal resection or endoscopic submucosal dissection. Endoscopic ultrasound prior to resection can be helpful to ensure there is no deep muscle layer involvement. If there is presence of lymph node involvement or the primary tumour appears advanced on imaging (T3 disease or greater) surgery can be considered. This would involve local resection if possible. The role of antrectomy is unclear in terms of causing regression of these lesions. However, can be considered in individual cases if recurrent large tumours are occurring. Medical therapy in terms of somatostatin analogues is generally reserved for patients with metastatic disease who have positive uptake on somatostatin based function imaging. There may also be a role for gastrin receptor antagonist netazepide, which has demonstrated anti-proliferative properties in gastric NETs. However, further studies are required.
DOI: 10.1530/endoabs.52.NETS6

NETS7
Refractory hypoglycaemia in advanced insulinomas
Maralyn Druce
Barts and the London School of Medicine and Dentistry, QMUL, London, UK.

Hypoglycaemia due to insulinoma, whether the tumour is advanced or not at the time of diagnosis may be difficult to treat. Profound and recurrent hypoglycaemia may be an important clinical problem for the patient, impacting on daily
activities, resulting in recurrent admissions or even preventing safe discharge from an inpatient setting. In this talk we will review the options available for treating hypoglycaemia due to insulinoma, considering the strengths and limitations of these therapies and examining the evidence base for their use.

Translational Science
NETS13

Abstract unavailable.

Debate: There is a role in resection of NET hepatic metastases - surgical dilemma
NETS11

Debate: There is a role in resection of NET hepatic metastases - surgical dilemma
Tom Armstrong
University Hospital Southampton, Southampton, UK.

Tom Armstrong will present evidence to support the role of surgical resection NET liver in the case based discussion detailed above.

DOI: 10.1530/endoabs.52.NETS11

Plenary Speaker & Trials update
NETS15

The evolving landscape in Nuclear Medicine in NETs
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A multidisciplinary team is responsible for the management of over 1,200 NET patients per year in our hospital. Tumor board decisions for peptide receptor radiotherapy (PRRT) are based on the Bad Berka Score which takes into account molecular imaging features and clinical aspects. The therapy plan for each patient is individualized. Retrospective analysis was performed in 1048 patients (age 4–85 years) with progressive NETs treated at our center since 2004 using Lu-177 (n = 331), Y-90 (n = 170) or both (n = 499). Follow up was up to 132 months. G1-2- NETs accounted for 54%. The median overall survival (OS) of all patients from start of PRRT was 52 months. A phase III multicentric, randomized, controlled trial (NETTER-1) has evaluated 177Lu-DOTA0-Tyr3-Octreotate (Lutathera®) in patients with progressive, somatostatin receptor positive midgut NETs. The primary endpoint was PFS per RECIST 1.1 criteria. Secondary objectives included objective response rate, overall survival, toxicity, and quality of life. Enrolment was completed in Feb-2015 (230 patients in 35 European and 15 US sites). The number of centrally confirmed disease progressions or deaths was 23 in the Lutathera group and 67 in the Octreotide LAR 60 mg group. The median PFS was not reached for Lutathera and was 8.4 months with 60 mg Octreotide LAR (95% CI: 5.8–11.0 months), P<0.0001, with a hazard ratio of 0.21 (95% CI: 0.13–0.34). Although data are not mature enough (13 deaths in the Lutathera and 22 in the LAR group), an improvement in OS appears very likely. PRRT lends a significant benefit in PFS (and presumably in OS). The combination of Lu-177 and Y-90 may be more effective than either radionuclide alone. Up to 10 cycles of PRRT, given over several years were tolerated very well by most patients. Severe renal toxicity can be avoided, myelotoxicity is usually mild. MDS occurs in approx. 3% of all patients treated. Quality of life can be significantly improved. PRRT may be effectively combined with TACE, SIRT, radiofrequency ablation (RFA), chemotherapy (e.g. using Capecitabine, Temozolomide), and kinase inhibitors. PRRT should be performed only at specialized centers as NET patients need highly individualized interdisciplinary treatment and long term care.

DOI: 10.1530/endoabs.52.NETS15
Oral Communications
**OC1**

A predictive quotient index, comprising neuroendocrine gene cluster analysis in blood and tissue grading is specifically predicting PRRT efficacy

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Background The efficacy of PRRT is based upon NET overexpression of somatostatin receptor (SSR) to deliver targeted isotope therapy. SSR expression (Krenning scale) compared to Predictive Quotient Index (PQI) (circulating NET transcript analysis mathematically integrated with grade) indicates the latter is more accurate for predicting PRRT efficacy. We evaluated whether PQI was specifically predictive or was prognostic for PRRT compared to other therapeutic strategies.

Methods We evaluated three treatment cohorts. 1Lu-PRRT-treatment (n = 146 (Rotterdam: Meldola; Bad Berka) and two Comparator cohorts. These comprised GEPNETs (n = 106, in a watch-and-wait program) and somatostatin analog (SSA)-treated GEP-NETs (n = 28). Blood prospectively collected. Baseline evaluations: Grade (Ki67) and NETest (qRT-PCR - multianalyte algorithmic analyses). All samples were blinded. The PQI (NETest genes regulating two 'omic' clusters metabolism and growth factor signaling) integrated with the Ki67 index. The PQI has two prediction outputs: 'PRRT-responder' (R) vs 'PRRT-non-responder' (NR). Disease control was by RECIST criteria (R (stable, partial and complete response) vs NR (disease progression)). Statistics: Kaplan-Meier survival analysis.

Results

PRRT cohort (n = 146). Median follow-up: 14–16 months. Cohort Meldola: mPFS for patients identified as ‘PRRT-responders’ was not reached versus 10.4 months (χ² = 38, P < 0.0001). Cohort Bad Berka: Not reached vs. 17 months (χ² = 27.4, P < 0.0001). The PQI accurately predicted response in 94-97% of PRRT-treated individuals. SSA cohort (n = 28). Median follow-up 11 months (9-15). No significant difference in mPFS was noted between ‘Responders’ and ‘Non-responders’. The PQI does not predict SSA response. Comparator cohort (n = 106). Median follow-up 19 months (1–36). No significant differences in median survival between ‘Responder’ vs Non-Responder (both mPFS: 24 months). The PQI was neither predictive nor prognostic in the comparator groups.

Conclusion An integrated measurement (PQI) of ‘omic’ NET gene analysis with grading in an individual tumor is a specific predictive marker for PRRT therapeutic efficacy in neuroendocrine tumors. DOI: 10.1530/endobas.52.OC1

**OC3**

Incidence and prevalence of neuroendocrine tumours in England

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Introduction Historically the incidence and prevalence of neuroendocrine tumours (NETs) has been difficult to establish due to issues with disease coding and data collection. Studies estimated the incidence of gastroenteropancreatic neuroendocrine tumours (GEP NETs) to be 1.3 per 100,000 per year (incidence hereafter given as cases per 100,000). However, the SEER USA data suggests a four-fold higher incidence, and prevalence of 35 per 100,000. This study aimed to identify the incidence and prevalence of NETs over a ten-year period utilising the Public Health England (PHE) population-based cancer registry.

Materials and methods Age-standardised incidence rates and prevalence from the 1st January 1995 to 31st March 2016 were calculated using data from the PHE National Cancer Registration and Analysis Service (NCRAS) database.

Results In 2015, the age-standardised incidence rate for NETs in England (excluding small and large cell neuroendocrine carcinomas, SCLC and LCNEC respectively) was 8.84, 8.37 in males (95% CI, 8.02-8.72) and 9.30 in females (95% CI, 8.49-10.11).
8.91–9.71) and; rising from 3.9 in 2001, with an average yearly increase of 0.39 cases. The incidence of SCLC was 7.72 and LCNECs was 0.44. The cohort was 90.1% White, 2.6% Asian, 1.8% Black, 1.4% other and 4.0% ethnicity unknown.
The most common primary tumour sites were: 20.2% colorectal, 19.5% lung, 14.1% small intestinal, 9.6% pancreatic, 6.9% skin, and 5.3% stomach. The stage breakdown was 23.3% stage I, 11.7% stage II, 14.2% stage III, 25.9% stage IV and 24.8% stage unknown in the 91.3% of the tumours with a histological confirmation from a primary, the remaining 8.7% were unknown primaries at diagnosis. The prevalence was 19,268 (34.9 per 100,000), 8,743 males and 10,525 females.

Conclusion
This study has clearly demonstrated that incidence of NETs in England is significantly higher than previously reported. The data demonstrate similar incidence and prevalence rates to those reported in the SEER database. Importantly, it highlights that colorectal and lung NETs are the most common primary sites.

Keywords: Neuroendocrine cancer; prevalence; incidence
DOI: 10.1530/endoabs.52.OC3

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Poster Presentations
P01
Genetics and diagnostic characterisation of bladder paragangliomas
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Bladder Paragangliomas (PGLs) are a rare manifestation of sympathetic chain PGLs and occur in prone patients with SDH mutation. They often display an aggressive phenotype with metastatic disease and require long-term follow up. SDHB immunostaining plays a significant role in initial risk stratification and facilitating appropriate genetic testing. We report four cases illustrating diagnostic management and outcome issues in this rare neuroendocrine pathology; two with SDHB mutation, 1 SDHA and 1 awaiting extended genetic analysis in view of young age (33 years). We anticipate a positive SDH mutation due to the anatomical location and pathogenicity. Our patients ranged from 29 to 67 years of age (median 42 years), 2M and 2F with predominant presentation being haematuria. Headache and sympathetic symptoms during micturition were also present in two patients. Plasma normetadrenaline was elevated in three patients and a second tumor gene was also identified in one who tested positive for SDHB mutation and subsequently developed metastatic disease. Initial biochemistry was not available in one patient as he underwent tumour resection in another centre several years ago. The tumours in all four patients displayed Met-Clinically although they are reported to have preference for FDG-PET and Gallium Dotatate. SDHB immunostaining is currently available in one patient only (67 year old lady) who tested negative in our initial routine genetic panel. However, she underwent screening for SDHA as the tumour sample repeatedly stained negative on SDHB immunohistochemistry indicating a likely mutation. SDHA frameshift variant Exon 2 c.133_136delinsCTT was identified which has not been previously reported in bladder PGLs. We conclude that SDHB immunostaining still remains an indispensable tool especially for the evaluation of bladder Paragangliomas. As new causative genes become validated, extended genetic panel should be included in screening bladder PGLs especially mutations involving all SDH and other genes involved in the regulation of citric acid cycle.

DOI: 10.1530/endoabs.52.P01

P02
Validation of a blood biomarker test for the diagnosis and management of bronchopulmonary neuroendocrine tumours
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Background
There is currently no effective blood biomarker for lung neuroendocrine neoplasia diagnosis and management. We describe the clinical utility of a 51 neuroendocrine-specific gene panel in blood to diagnose bronchopulmonary neuroendocrine tumors (BPNETs) and define their clinical status.

Methods
The discovery set included BPNETs (n = 154) and controls (n = 90), randomly assigned (1:1) to a test and validation set. Specificity was evaluated in: lung adenocarcinoma (n = 54) and squamous cell carcinoma (n = 37), other neuroendocrine neoplasia (n = 13), and COPD (n = 18). We assessed clinical efficacy: disease presence versus absence in a surgical cohort (n = 45) and progressive versus stable disease (n = 154). We measured gene expression (real-time PCR) and chromogranin (ELISA-Euro Diagnostica). Gene expression and CgA levels were evaluated by non-parametric, ROC, Fisher’s test and decision curve analysis.

Findings
Control gene levels were 6.6 ± 2.5 in healthy volunteers and elevated in test (47.3 ± 3.6) with sensitivity and specificity of 34% and 99% (n = 37), 82% and 99% (n = 13), and 89% and 99% (n = 18). The AUC for differentiating carcinoids from controls was 0.98 ± 0.01. Levels were elevated in other lung neuroendocrine neoplasia (59 ± 5%) but were low in non-neuroendocrine lung cancers (25 ± 3%) and COPD (23 ± 8.5%). Progressive disease (n = 49) was significantly higher (72 ± 23%; P < 0.0001) than stable disease (n = 10; 33 ± 17%). The AUC for differentiating progressive/stable was 0.89 ± 0.03. Tumor resection significantly decreased scores (70 ± 7% to 23 ± 3%, P < 0.0005). Levels in surgical recurrent or residual disease remained elevated: 66 ± 8%. CgA was elevated in only 38% of carcinoids and levels were unrelated to clinical status (AUC: 0.51 ± 0.05). Decision Curve Analysis confirmed the utility of gene expression analysis (net benefit > 75% to a disease risk threshold of 0.92 vs < 30% for CgA).

Interpretation
NET-specific gene measurement in blood accurately diagnoses bronchopulmonary carcinoid neoplasia. Gene expression levels identify the effectiveness of surgery and distinguish stable from progressive disease.

DOI: 10.1530/endoabs.52.P02

P03
Blood measurements of Neuroendocrine Tumor (NET) transcripts and gene cluster analysis predict efficacy of PRRT
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Background
Peptide receptor radionuclide therapy (PRRT) is based on somatostatin receptor (SSR) overexpression to deliver targeted isotope therapy. Functional imaging of SSR expression (SRE) is used as a predictor of efficacy, but there is no method to objectively predict PRRT efficacy. We report the efficacy of Predictive Quotient Index (PQI) to predict the utility of PRRT. PQI is derived from circulating NET transcript analysis (NETest) integrated with the tumor grade. We validated the utility of this PRRT complementary diagnostic in a prospective, blinded study conducted at Rotterdam.

Methods
NETs (n = 42); with progressive disease (74%) were treated with 177Lu-PRRT-treated (29.1 ± 2.2 Gbq). Baseline evaluations included clinical status, Grade (Ki67), SRE, CgA (NeoLisa, ULN > 108 nmol/l) and NETest (qRT-PCR - multianalyte algorithmic analyses, NETest score: 0–100%; UNL > 14%). The PQI (a calculation of ‘omic’ NETest genes regulating metabolism and growth factor signaling) is mathematically integrated with tissue Ki67. The PQI has two prediction outputs: ‘responder’ (R) vs ‘non-responder’ (NR). Disease assessment was by RECIST criteria (Partial Response and Disease Stabilization = Responder vs Disease Progression = NR). All samples were blinded. Statistics: Cox proportional multiple regression, Kaplan-Meier survival, & McNemar-test.

Results
At restaging, the overall response (disease control rate) was 76%; median PFS not reached (follow-up 5–20 months). Histology: GI: 12; GI: 21; GII: 2; and lung: TC: 2; AC: 4; SRE was Grade 3 (in 80%). NETest was elevated in (NETest score: 61 ± 22%) in all. Predictive accuracies of baseline SRE, clinical status, and CgA ranged from 25% to 54% (not-significant). PQI was the only predictive marker by multivariate analysis (P = 0.001). The PQI diagnostic was 95% concordant with response to therapy and significantly more accurate than other markers (McNemar: P = 0.002). Cox proportional modeling confirmed PQI utility (OR: 9.1, P < 0.004). K-M analysis identified significantly different mPFS between R (not reached) and NR (10.4 months; Hazard Ratio: 92, P < 0.0001).

Conclusion
The predictive quotient index comprising blood based ‘omic’ analysis and tissue grading when measured prior to therapy predicts the efficacy of PRRT therapy in GEP and lung NETs in 95%.

DOI: 10.1530/endoabs.52.P03

P04
A liquid biopsy for the diagnosis and monitoring of bronchopulmonary/lung carcinoid
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Background
No effective blood biomarker exists to detect and clinically manage bronchopulmonary (BP) neuroendocrine tumors. We developed a blood-based

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51 neuroendocrine tumor (NET)-specific transcript set to diagnose and monitor gastroenteropancreatic NETs. In this study, we examined whether the signature functioned in lung NETs. Thereafter, we examined performance metrics to assess clinical utility. The multianalyte gene signature accurately diagnosed the tumor and in addition differentiated stable from progressive disease as determined by RECIST criteria.

**Methodology**

Gene expression was evaluated in: i) publicly-available BPNET transcriptomes (GSE53679); ii) two BPNET cell lines; and iii) BPNET tissue with paired blood ($n=7$). A pilot study assessed blood gene expression in 25 small bowel NETs and 25 BPNETs and a separate validation study in age- and gender-matched BPNETscontrols ($n=25$ each) was undertaken. Gene expression measured by real-time PCR was scored (0-100%); normal: <14%. Data was assessed by regression analyses, hierarchical clustering, Fisher’s and non-parametric evaluations.

**Results**

All 51 genes were identified in BPNET transcriptomes, tumor tissues and cell lines. Significant correlations were evident between paired tumor and blood ($R^2=0.63–0.91, P<0.001$). In the pilot study, blood gene expression was highly correlated ($R^2=0.91, P=1.7×10^{-17}$) between small bowel NET and BPNET. In the validation cohort, all 25 BPNETs exhibited a positive score compared to only 20% of controls ($P<0.0001$). Transcript scores were significantly elevated ($P<0.0001$) in BPNETs (57±28%) compared to controls (4±5%). BPNETs with progressive disease (83±11%) exhibited higher scores than stable disease (32±7%, $P<0.0001$).

**Conclusion**

Blood measurements of NET-specific genes accurately diagnosed bronchopulmonary carcinoids and distinguished stable from progressive disease. We envisage this marker panel to have clinical utility as a liquid biopsy able to identify disease and monitor progression in real-time.

DOI: 10.1530/endoabs.52.P04

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**P06**

**Nutritional assessment and vitamin deficiencies in patients with NETs**

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**Introduction**

Neuroendocrine tumours (NETs) have diverse natural history and clinical syndromes. As a result of the disease or related to management, patients may have altered gut or pancreatic function that can cause nutritional deficiencies. There is a lack of consistent evidence-based dietary guidance for patients with NETs.

**Aim**

This study evaluated whether nutritional status and nutritional deficiencies had been assessed in patients with NETs in an existing service in South Wales.

**Method**

A retrospective study included 141 NET patients seen in Gastroenterology ($n=74$) and Endocrinology ($n=67$) clinics. Key parameters collected were: BMI, weight, vitamin B12, Ferritin, Folate, Albumin, vitamins A/D/E and presence of steatorrhoea. Evidence of treatment with vitamin or iron replacement and use of bile acid sequestrants or Creon was also recorded.

**Results**

Weight was recorded in under half of patients (70/141) and BMI in just 14% ($n=20$). This rose to 100 and 73% respectively in patients seen by a gastro-specialist dietitian; only 22 patients (16%) had this specialist input. Fifty four patients reported weight loss, 70% of these ($n=38$) had a quantified weight loss, 46% a percentage weight loss calculated. One hundred and six patients (75%) had been investigated for a form of vitamin or iron deficiency. The likelihood of investigation was significantly higher in Gastroenterology clinic patients than Endocrine clinics (95% vs 54%, $P<0.01$). 57% of those investigated were found to have a deficiency, which was consistent across specialities: 59% (41/70) of those from Gastroenterology clinics and 53% (19/36) from Endocrine clinics. 41/60 patients (68%) with a recorded deficiency did not have sufficient replacement. 7/27 patients with iron deficiency were given supplementation. Thirty eight patients had vitamin D levels tested (27%), 29 were insufficient (76%). Twenty seven patients reported steatorrhoea, 26 of whom were prescribed somatostatin analogues. 96% of these patients were also prescribed Creon.

**Conclusion**

Although higher rates of nutritional assessment were found in patients who had been assessed by Gastroenterology and with gastro-specialist dietetic involvement, assessment and management of nutritional status in patients with NETs remains an unmet need. Further evidence is required to evaluate nutritional assessment in NETs.

DOI: 10.1530/endoabs.52.P06

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**P07**

**Piloting a group programme aiming at psychologically supporting neuroendocrine patients**

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**Background**

The median survival for patients with metastatic neuroendocrine tumours is greater than 5 years. Despite a heavy burden of metastatic disease and an incurable diagnosis many patients continue with a relatively normal lifestyle. Vast amounts of time and money is spent on diagnosing and treating the physical aspects of cancer but little is currently available to help with the psychological wellbeing of our patients. As NET nurses we spend large amounts of our time talking to patients. Much of this contact is directed at alleviating anxiety surrounding diagnosis, investigations and treatment. Despite our efforts for some, there is a continual cycle of stress and anxiety fuelled by periodic scans, clinical episodes and episodes of treatment. This anxiety limits quality of life. Ironically it’s this ‘quality of life’ we are attempting to maintain with our medical intervention.

**Method**

In Dorset we have set up a group programme study to psychologically support Neuroendocrine patients. Each group consists of 6–8 patients all with neuroendocrine tumours all requiring follow up from the neuroendocrine service. Each patient is selected by the NET nurse and asked if they felt they required further psychological support. Selection is based on recent conversations with patients either face to face or over the telephone. Patients are then contacted by programme psychotherapist and current psychological needs discussed. One to One interviews are then arranged for the Psychotherapist to speak face to face.
to the patients. For each group 6 sessions are set up to be held weekly. The group meetings are scheduled and adapted to address the individual needs of the patients. Sessions focus on giving the patients tools in order to manage their anxiety and stresses going forward into the future. The sessions included visualization, centralisation, relaxation and mindfulness. These sessions may touch on other aspects such as exercise and benefits it also included visit from a nutritionist all of which patients said caused them additional stress and anxiety.

Results
Patient feedback and quality of life data from the first group pilot will be presented.

Conclusion
The psychological impact of a diagnosis of neuroendocrine tumour cannot be underestimated.

DOI: 10.1530/endoabs.52.P08

P08
Audit of a new nurse-led non-medical prescribing (NMP) clinic for systemic anti-cancer agents (SACTs)
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The number of people diagnosed and living with cancer in the UK continues to rise and this also places increasing demands on specialist cancer care services (NHS England 2015). Neuroendocrine Tumours (NETs) incidence and prevalence increases alongside this demand (PHE 2016). NETs still remain a rare cancer with specialist needs and the clinical nurse specialist (CNS) team are ideally placed to support these patients. Oncology clinics are becoming increasingly pressured and the need to think of innovative ways of reducing pressure whilst maintaining and enhancing the patients experience is important. In order to address this we set up a nurse-led SACT NMP clinic alongside the oncology clinic to improve patient experience and reduce oncologist clinic review.

Aims/objective
To assess the impact of the NMP nurse-led clinic on the patient and the NET service.

Methodology
Questionnaires were sent out either via email or given in clinic to patients after 3 months of the nurse clinic starting. A questionnaire was also given to all oncologists within the clinic and also to the oncology pharmacist for analysis.

Results
29 SACT NMP prescriptions for 15 patients were prescriptions. The nurse prescribed targeted agents (Sunitinib and Everolimus) and IV Chemotherapy regimes (Carboplatin, FCIST and PCarlboSo). Patient Feedback: 14/15 completed patient experience questionnaire: Quality of nurse review Excellent- 84%, Confidence in Nurse knowledge- 100%. Patients felt involved in decision making- 100%. How satisfied were patients with experience- 57% extremely satisfies, 43% very satisfied. Clinician feedback: - Was safe practice observed – 100% yes, Was decision making by the NMP appropriate and safe – 100% yes. Felt more time for the medical team to review other patients – 100% yes.

Discussion
The experience for this nurse-led clinic is very positive; benefitting patients experience and consultants. The nurse felt increased satisfaction in her role taking part in this clinic. The audit highlights that with experienced NET CNS’ and NET physicians this is a viable model for enhancing patient care.

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P09
Audit of South Wales Neuroendocrine MDT pathology reports
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The South Wales regional NET Multidisciplinary Meeting (MDT) discusses patients on a monthly basis. The European Neuroendocrine Tumour Society (ENETS) have guidance on expected pathology input into a NET MDT service. We assessed pathology reports submitted and discussed in 2016 for compliance with ENETS criteria, and determined the time from pathology reporting to MDT discussion. 117 patients had pathology submitted for review in 2016 and were assessed by one specialist NET pathologist. Of these, 105 pathology reports were available for audit, consisting of 60 biopsies and 45 surgical samples that were 55 and 11% complete respectively. Overall, only 36% of reports were complete. 26% of cases were submitted and discussed within one month of reporting, 62% taking 2–9 months to be submitted, and 12% were historical diagnoses for review.

Conclusion
Completeness of pathology reports are below the target level (36% vs target 100%). Surgical cases are particularly poor (11% complete). Time from reporting to referral was below standard with only 26% being discussed at the next MDT.

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P10
Neuroendocrine Tumour (NET) patients experiences of support in the community setting across the cancer treatment trajectory
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Background
Neuroendocrine tumours (NETs) and carcinomas (NECs) are a heterogeneous group of malignancies, with no common clinical pathway, but previous study has highlighted a common need for effective, well-timed support. There is geographic variation in the availability and provision of specialist NET cancer services across the UK and this is reflected in the diverse patient experiences reported.

Service improvement
To improve the patients journey, the NET Patient Foundation are developing the Support Nurse service, to provide the support patients have identified as being the most appropriate, at the times when it was most needed and signpost to available allied services.

Aim
The aim of the study is to explore the changing nature of support requirements throughout the patient journey and identify sources, with optimal timings, of effective patient support.

Methodology
A focus group approach has been chosen as it is particularly useful where it is important to highlight common experience, or identify different views. The data will be collected in July 2017 from 3 to 4 focus groups at different locations in England and Wales, consisting of 4–8 NET patients and using a pre-determined, structured sequence of questions in a focused discussion.

Results
The data will be analysed using an inductive qualitative content analysis process. Discussion
The themes identified by the analysis of the focus group discussions will define further study and inform the discussion of an optimal support strategy that can be tailored for each individual patient.

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P11
The Missing Malignancies - Follow up of patients with pulmonary carcinoid tumours in the UK: Results from the National Lung NET Pathway ('LEAP') project
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Introduction
Close long-term follow-up of patients with pulmonary carcinoid (PC) tumours is important for detection of recurrence, which can occur many years after primary surgery. Expert consensus guidelines for management of PC were published in 2015 (European Neuroendocrine Tumour Society (ENETS)) and provide recommendations for follow-up type, frequency and duration. The LEAP Project aimed to describe current follow-up practices in the UK following publication of the guidance, to inform future service improvements.

Methods
Between October 2016–May 2017 face-to-face or telephone surveys were conducted with 27 lung NET clinicians from 27 UK centres, including all ten UK ENETS Centres of Excellence. Clinicians were asked about their current practices for follow-up of patients with PC after completion of initial treatment.

Results
Thirteen medical oncologists, six clinical oncologists and eight other specialists participated in the survey. The respondents were from centres with an estimated 250–500 PC patients under current management and 2–80 new patients/year. Initial follow-up frequency in PC patients following completion of initial surgical treatment ranged from 2-monthly to annually. Follow-up duration ranged from 2-years to indefinite according to disease stage. The proportion of respondents
P12

1-Year survival rates for neuroendocrine tumour patients in England

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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.

Materials and methods

NET patient survival was calculated for England using the Public Health England (PHE) National Cancer Registration and Analysis Service (NCRAS) dataset which captures tumour stage during TNM staging. Stage was based on dysplasia and morphology. The Kaplan-Meier survival method was used to analyse overall death in 12,755 patients diagnosed with a NET between 2013 and 2015.

Results

The 1-year overall survival was 75% for NETs (95% CI, 74.5–76.1), 72% in males vs 79% in females (P < .001). Survival by age group was as follows: 0–55 years 90% (95% CI, 89.2–91.2); 56–65 80% (95% CI, 78.3–81.4); 66–75 71% (95% CI, 70.0–72.9); > 75 60% (95% CI, 57.9–61.5) (with P < .001 for comparisons between all age groups). Survival decreased with increasing grade (1/2 and 3) and stage (1, 2, 3, and 4 respectively). Cotrocetal (n = 2712):

Grade 1/2 (excluding Mixed adenoneuroendocrine carcinoma (MANEC)): 99% (97.6–99.4); 97% (93.9–98.3); 95% (94.5–97.7); 80% (72.9–86.2)
Grade 3 (excluding MANEC): 89% (70.4–96.4); 90% (72.9–96.8); 67% (56.3–76.2); 22% (16.3–27.9)
MANEC: 98% (85.8–99.7); 97% (92.3–99.2); 85% (74.4–91.8); 60% (45.2–72.6)
Overall (including unknown stage): 88% (85.6–88.9)

Lung (n = 2,460, excluding *small and large cell lung cancer):

Grade 1/2: 98% (97.2–99.1); 98% (97.3–99.6); 93% (82.9–97.4); 69% (59.1–76.8)
Grade 3: 93% (89.4–95.6); 81% (71.4–88.2); 63% (55.0–70.7); 26% (22.5–30.0)
Overall: 74% (72.7–76.2) in comparison, *SCLC (n = 2712):

Grade 1/2: 97% (96.7–98.7); 95% (88.8–97.9); NK; 85% (79.7–89.6)
Grade 3: 87% (68.3–94.8); 87% (58.6–96.7); 56% (30.5–74.7); 42% (35.9–48.9)
Overall: 81% (78.3–82.8)

Small bowel (n = 1,088):

Grade 1/2: 98% (90.8–99.4); 96% (89.7–98.5); 96% (93.6–97.3); 88% (84.3–90.7)
Grade 3: NK; NK; 83% (60.1–93.1); 72% (60.5–80.5)
Overall: 99% (88.6–91.5)

Conclusion

The survival results show that tumour grade has the potential to be a good prognostic indicator for all types of NET. This is the first large series regarding MANEC demonstrating poor outcomes.

Keywords: Neuroendocrine cancer; survival; grade; stage; age

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P13

Metachronous primary cancers in neuroendocrine tumour patients

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Introduction

Historically there has been an association with neuroendocrine tumours (NETs) and other cancers. However, this has not previously been well characterised. We aimed to determine the incidence of second malignancies in patients with NETs and investigate any association of the anatomical site of NETs with other malignancies.

Materials and methods

12,844 patients were diagnosed with a NET between 2013 and 2015 and captured by the National Cancer Registration and Analysis Service (NCRAS). A count of tumours per person, and the most common sites for second malignancies were made. The relative cancer site-specific NETs after non-neuroendocrine cancer was investigated.

Results

Of the 12,844 people in the analysis, 2,805 (21.8%) had at least one NET or non-NET, metachronous or synchronous cancer comprising: 2,311 patients with two cancers: 424 with three cancers; 61 with four cancers; seven with five cancers; and two with six cancers. The most common sites for metachronous cancer primaries were prostate (14.4%), breast (13.4%), non-melanoma skin cancer (12.0%), colon (11.4%), lung (5.5%), lymphoma (4.7%), kidney (3.8%), melanoma (3.4%), bladder (3.4%), rectum (3.3%), ovary (2.4%), endometrium (2.4%), leukaemia (2.0%), stomach (1.3%), thyroid gland (1.3%) and pancreas (1.1%). Eighty-one percent of patients had a second primary post-NET diagnosis, 12% had a second primary post-NET diagnosis and 7% had a synchronous secondary. For males who had previously been diagnosed with prostate cancer the risk of site-specific NETs were as follows: bladder NET (RR 1.47 (CI: 0.98–2.21)); rectal NET (RR 1.47 (CI: 0.98–2.21)); and pancreatic NET (RR 0.99 (CI: 0.73–1.36)); and small intestinal NET (RR 1.08 (CI: 0.84–1.36)).

Conclusion

Based on a large national cancer registry, most patients with NETs who presented with second cancers had pre-NET non-neuroendocrine primary cancers. This study identified prostate cancer as the most common site in male NET patients, and a possible association between prostate cancer and bladder neuroendocrine cancer needs further exploration.

Keywords: Neuroendocrine cancer; second primary; metachronous cancers; synchronous cancers

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P14

Efficacy and safety of telotristat ethyl in patients with carcinoid syndrome inadequately controlled by somatostatin analogs: Analysis of the completed TELESTAR extension period

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Background

The phase III, placebo-controlled, randomized TELESTAR study evaluated efficacy and safety of telotristat ethyl (TE) in patients (pts) with diarrhea (≥ 4 bowel movements (BMs)/day) due to carcinoid syndrome (CS) inadequately controlled by somatostatin analogs (SSAs). TE, a tryptophan hydroxylase inhibitor, decreases peripheral serotonin levels. As add-on treatment to SSAs, TE 250 mg 3x/day (tid) and TE 500 mg tid significantly reduced BM frequency (P < 0.001) compared with placebo over the 12-week Double-blind Treatment (DBT) period. After Week 12, pts crossed over to a 36 week Open-label Extension (OLE) period with TE 500 mg tid; data from the full 48 weeks are presented.

Methods

Changes from baseline in BM frequency (monitored weekly), urinary 5-hydroxyindoleacetic acid (u-5HIAA; Weeks 18, 24, and 48), European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTCQLQ-C30) score (Weeks 24 and 48), and safety during the OLE period were evaluated.

Results

Of the 135 pts randomly assigned, 118 completed the DBT period; 115 pts subsequently entered (and 79 completed) the OLE period. Of the 36 pts who discontinued the OLE period, the most frequent reasons were adverse event (AE; 15 pts) and withdrawal of consent (9 pts). Treatment-emergent AEs led 18 pts to discontinue TE; gastrointestinal disorder was the most commonly reported reason (6 pts). Reductions from baseline in BM frequency (~ 2 BMS/day) and u-5HIAA levels (range −20.0 mg to −49.5 mg/24 hours) during the OLE were consistent with the results of the DBT period and persisted through Week 48. Improvement in EORTCQLQ-C30 diarrhea subscale scores relative to baseline (range −18.8 to −30.6 points) was notable and persisted through Week 48. Crossover into the OLE period was well tolerated. Treatment-emergent AEs were mainly mild to moderate and occurred at a similar rate as in the DBT period.

Conclusions

Patients benefited from TE throughout the OLE period. TE was well tolerated over 48 weeks and its efficacy was consistent with previously reported data.

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P15


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Introduction

Platinum-etoposide chemotherapy is a globally established chemotherapy combination for EP-G3-NEC. However, there are many different schedules for such chemotherapy, and the preferred one for EP-G3-NEC has not been established.

Methods

An international survey was created, and completed by colleagues with an expertise in the field of neuroendocrine neoplasms. The aim was to explore which schedules of platinum-etoposide chemotherapy are used across centres and to assess consistency in clinical practice.

Results

Sixty-four replies were received (June-August’17); completed by medical oncologists (43;67.2%), clinical oncologists (11;17.2%), gastroenterologists (8;12.5%) and endocrinologists (2;3.1%). United Kingdom was the most represented country (25;39.1%), followed by Spain (13;20.3%). Most of the physicians completing the survey (39;60.9%) had ≥ 10 years of experience in the field. 29 (46.0%) were working in European Neuroendocrine Tumor Society (ENETS) Centres of Excellence (COE). A small minority did not take KI67 (7;11.1%) or morphology (7;10.9%) into consideration when selecting type of chemotherapy to be administered. Regarding choice of chemotherapy, most (61.95.3%) agreed on selecting platinum-etoposide chemotherapy as first-line treatment for NEC tumours ≤ post-differentiation ≥ Ki67 > 55%; although there was a large number of different schedules used: cisplatin-based (28;80.64.7%), carboplatin-based (32;90.33.3%). Most centres chose a schedule with intravenous etoposide (53;80.88.3%), while oral etoposide was less popular (77;86.11.4%). Chemotherapy was usually administered up to a maximum of 6 cycles (49;79.0%). At time of progression, choice of second-line chemotherapy was influenced by the time between completion of first-line chemotherapy and tumour progression. When this period was > 6 months, re-challenge with platinum-etoposide was the preferred choice (29;46.0%). Conversely, when time to progression was ≤ 6 months, platinum-etoposide was not considered by any of the physicians as an option for second-line chemotherapy (0%), and alternative combinations such as fluoropyrimidine/trimetrexate (21;34.4%) and temorolomide/capetebatine (18;29.5%) were preferred.

Conclusions

Although there appears to be consensus in selection of platinum-etoposide based chemotherapy for first-line treatment for patients with advanced EP-G3-NEC, significant variation in the exact regimen employed across different institutions exists. Prospective studies in this patient population are required in order to standardise practice.

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P16

Relationship between symptoms and health-related quality of life benefits in patients with carcinoid syndrome: post-hoc analyses from TELESTAR

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Background

The safety and efficacy of telotristat ethyl (TE) in patients (pts) with metastatic neuroendocrine tumors (NETs) and carcinoid syndrome (CS) not adequately controlled with somatostatin analogs (SSAs) have been demonstrated. TE-treated pts showed significantly greater reductions in bowel movement (BM) frequency and more presented with durable response than placebo (PBO)-treated pts. These post-hoc analyses examined the relationship between improvements in symptoms and health-related quality of life (HRQoL) in pts who were durable responders (DRs; n = 48) and non-durable responders (NDRs; n = 87), irrespective of treatment group, in TELESTAR (NCT01677910).

Methods

Pts were randomized 1:1:1 to TE 250 mg, 500 mg, and PBO three times daily during the 12-week (wk) double-blind (DB) treatment period; durable response was predefined as a daily BM frequency reduction of ≥ 50% from baseline for ≥ 6 months, or ≥ 30% from baseline for ≥ 6 months. BM frequency was measured daily.

Results

135 pts were randomized, 45 in each group. The mean difference (95% CI) in change from baseline between DRs and NDRs at Wk12 was (1.8 (−2.3, −1.2)
for daily BM frequency, (−1.2 (−1.6, −0.7)) for daily flushing, (−38.7 (−70.0, −7.3)) mg/24 hrs for u5-HIAA levels, (−1.2 (−1.8, −0.6)) for abdominal pain severity and (−0.3 (−0.4, −0.2)) for urgency to defecate. DRs showed meaningful and/or significant improvements in QLQ-C30 global health (8.1 (−0.3, 16.5)), summary score (4.9 (0.6, 9.2)), social functioning (5.1 (−4.7, 14.9)), nausea/vomiting (−7.5 (−15.4, 0.4)), pain (−16.0 (−27.0, −5.0)), diarrhoea (−14.7 (−26.5, −2.9)), and GINET21 gastrointestinal symptoms (−9.3 (−16.3, −2.2)) versus NDRs.

Conclusions
Durable response was associated with reductions in the symptoms and overall clinical burden of CS. DRs showed significant and/or meaningful improvements in global HRQoL, nausea, pain, diarrhoea, and gastrointestinal symptoms.

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P17 Surgical therapy for appendiceal neuroendocrine tumours: is appendectomy adequate?
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Background
Neuroendocrine tumours of the appendix (ANET) are relatively indolent tumours typically identified incidentally at surgery for suspected appendicitis. The role of right hemicolecystomy (RH) for tumours with ‘high risk’ features is debated. We compared the management of ANET at three centres against ENETS criteria for therapy selection.

Methods
Retrospective review of all patients diagnosed with ANET at three tertiary centres. Patients that underwent appendectomy alone or as part of another abdominal operation were reviewed – patients with histologically confirmed ANET were identified. All other histology types were excluded. Patient demographic, operative, biochemica/radiological, and follow-up data were extracted from a prospectively maintained database.

Results
Of 14,850 patients undergoing appendicectomy, 215 (1.45%) were diagnosed with ANET. There were 85 males (39.5%) and 130 females (60.5%). Regarding index operation, 193 (89.8%) underwent completion hemicolectomy (n = 15), no patient exhibited any evidence of recurrence: 5- and 10-year OS was 99.8% (95%CI 99.5%–100%) and 99.3% (95%CI 98.9%–99.7%), respectively (data for five patients was not available).

Conclusion
ENETS guidelines appear to identify patients at higher risk of nodal metastasis, however the oncological relevance of lymph node metastases in ANET is questionable. In most patients with ANET, right hemicolecystomy may represent over-treatment.

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P18 Circulating Tumour Cells (CTCs) are associated with bone metastases in patients with Neuroendocrine Tumours (NET)
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Background
Bone metastases have been described in up to 15% of patients with NETs and are associated with a worse clinical outcome. Here we investigate the role of CTCs as a marker of bone metastases in a large cohort of patients with gastroenteropancreatic NETs.

Methods
To be eligible for the study, patients were required to be ≥ 18 years old, have histologically confirmed midgut or pancreatic NET (pNET) and metastatic disease measurable by RECIST. Data were collected on age, gender, primary site, grade, metastatic sites and previous treatments. Patients provided 7.5 ml blood samples which were collected into CellSave tubes, maintained at room temperature and processed within 96 hours of collection. The CellSearch platform was used for detection and enumeration of CTCs by two independent operators, as previously described.

Results
Between 2009 and 2017, 251 patients with metastatic NETs were recruited from the Royal Free Hospital including 128 patients with pNET and 123 with midgut NET. Of patients with pNETs, 38% had CTCs detected with a mean of 11 CTCs per 7.5 ml of blood (range 0–430). Bone metastases were reported in 29 pNET patients (25%) and were significantly associated with CTC presence (P < 0.0001). There was no association between lung, peritoneal or lymph node metastases and CTC presence. Of patients with midgut tumours, 52% had detectable CTCs with a mean number of 15 (range 0–636). Bone metastases were reported in 36 midgut patients (29%) and were significantly associated with CTC presence (P = 0.02). There was no association between grade, lung, peritoneal or lymph node metastases and CTC presence. In both midgut and pNETs, the association between bone metastases and CTC presence was confirmed by logistic regression analysis and was independent from grade as well as from other sites of metastases.

Conclusion
Presence of CTCs measured by CellSearch is associated with bone metastases in NET patients. CTCs will be further analyzed for expression of markers involved in the molecular mechanisms underlying skeletal metastasis.

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P19 Mixed Adeno-Neuroendocrine Carcinoma (MANEC): a multicentre retrospective study
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Introduction
MANEC is a rare diagnosis and little is known on its epidemiology/prognosis/management.

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Methods
Demographic/clinical-pathological/survival data of patients with a diagnosis of MANEC (2010 WHO criteria) from five European centres were retrospectively reviewed.

Results
Sixty-six patients were identified (09/08-07/17); median age: 62.5 years (range 34–89); male: 66.7%; ECOG-PS 0–1: 59%; primary tumours from: small/large bowel 62.1%, oesophagus/stomach 22.7%, pancreas/biliary tract 13.6%, unknown 1.5%; adult-comorbidity-evaluation (ACE)–27 score 0: 36.4%. The median Ki-67 value of 70% (95%–Confidence-Interval (CI): 60–73.6). Most frequently expressed IHC markers were: synaptophysin (87.9%), chromogranin-A (CgA) (54.5%) and CDX2 (48.5%). Histology from recurrent/metastatic sites (14 patients) was PD-NE in 71.4%. Median follow-up time was 11.5 months (mo). Of 34 (51.5%) patients with localised-stage (LA) disease, 91.2% had curative surgery (22.5% had neoadjuvant chemo-radiotherapy (CT-RT), 29% had adjuvant or peri-operative CT), 5.9% had definitive CT-RT and 2.9% had unknown management; 77.4% recurred. Fifty-four (81.8%) patients were treated for advanced-stage (adv) disease; 50% had platinum-based CT, 5.5% irinotecan-based CT, 1.8% gemcitabine, 1.8% 5-fluorouracil/leucovorin, 3.7% unknown CT regimen, 1.8% CT-RT, 1.8% RT, 24% best-supportive-care (BSC), and 9.25% unknown management. Median overall-survival (OS) for all patients was 16.2 mo (95%–CI 12.1–21). Median recurrence-free-survival and OS in patients with LA disease were 12.9 mo (95%–CI 6.7–21) and 21 mo (95%–CI 9.6–19.4). On univariable analysis, age < 70 years and ACE-27 score 0 (vs 2–1) were prognostic for better OS (both P < 0.05); BIC negativity and CgA and first-line active treatment (vsBSC) were prognostic for better PFS (both P < 0.05).

Conclusion
This is one of the largest series of MANEC in current literature. PD-NE is predominant in both primary tumours and recurrent/metastatic sites. Survival outcomes are poor. Curative surgery is the preferred choice for LA patients. Platinum-based CT is the most frequently offered strategy in the adv setting.

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P20
Prophylactic right hemicolectomy in Appendiceal Neuroendocrine Neoplasms: challenging the current indications
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Introduction
To prevent loco-regional recurrence and subsequent development of distant metastases in Appendiceal Neuro-Endocrine Neoplasms (ANEN), the existing Guidelines have suggested several criteria for a prophylactic right hemicolectomy, following the initial appendectomy. However, some of those criteria seem rather arbitrary and have not been validated by large studies.

Aim
To assess the outcomes of prophylactic right hemicolectomy (RHC), focusing on regional lymph nodal invasion.

Materials and methods
Over a 10-year period, 263 patients with ANEN were identified. Patients with ‘goblet cell tumours’ or ‘mixed adenoneuroendocrine carcinomas’ were excluded. Patients who underwent RHC were categorized into Group A (GA): those with lymph nodal invasion (LNI) at RHC, and Group B (GB): those with without LNI. The original tumour size, tumour location, margin invasion, proliferation rate, meso-appendiceal invasion (MAI), as well as angioinvasion and lymph vessels invasion were assessed.

Results
Based on Guidelines’ recommendations, 72/263 (27%) patients underwent prophylactic RHC. GA included 23 patients (32%), and GB had 49(68%). All patients from both groups had R0 appendectomy. 30.5% tumours from GA and 45% from GB were measuring less than 1 cm, 30.5% from GA and 31% from GB were measuring between 1 and 2 cm. Whilst 39% from GA and 24% of GB, had tumours measuring more than 2 cm. Location at appendiceal base was demonstrated in 22% from GA, but only in 8% from GB. Deep (more than 3 mm) MAI was noted in 13% of GA and in 6% of GB. Angioinvasion and lymph vessel involvement were demonstrated in 30 and 57% from GA, in comparison with 10% and 8% from GB, respectively. Finally, 35% patients from GA and only 2% of GB had grade 2 tumours.

Conclusion
A significant percentage of patients had lymph nodal invasion at the time of prophylactic RHC for ANEN. Grade 2 tumours, angioinvasion and lymphatic invasion, location at appendiceal base and size more than 2 cm seem to be the most important risk factors. Larger studies with prolonged follow-up are needed, to identify the actual role of lymph nodal invasion to the overall disease prognosis.

Keywords: appendix; Neuroendocrine neoplasm; lymph nodes metastases; appendectomy; right hemicolectomy

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P21
Carboplatin-etoposide chemotherapy for patients with advanced extra-pulmonary (EP) poorly differentiated (PD) neuroendocrine carcinoma (NEC): outcomes from a European Neuroendocrine Tumour Society Centre of Excellence
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Introduction
Platinum-etoposide is considered standard-of-care first-line treatment for patients diagnosed with advanced EP-PD-NECs. The optimal platinum-etoposide schedule remains undefined; carboplatin is often substituted for cisplatin, although quality data is lacking.

Methods
Electronic records of patients with advanced EP-PD-NEC treated with carboplatin-etoposide (06/09-02/17) were reviewed retrospectively, with aim to provide real-life efficacy/safety data on carboplatin-etoposide in this setting. Chi-square test, Kaplan-Meier and univariate/multivariable Cox-regression analyses were performed, as appropriate.

Results
Seventy-three patients were screened, 57 eligible; median follow-up 8.57 months (mo); median age 70.4 years (range 36.2–88.4). Most patients were male (68.4%), had Eastern-Cooperative-OncoLoogy-Group performance-status (ECOG-PS) 0–1 (79%) and none/mild comorbidities (72%). Stage of primary tumour: foregut 35.1%, hindgut 24.6%, unknown 21%, pancreas 8.8%, others 10.5%. Most had stage IV disease (87.7%); median number of metastatic sites: 2 (range 1–6), liver (68%) being the most common. Histopathology: median Ki-67 73% (95%–Confidence-Interval (95%–CI) 60–80%); morphology included small-cell (33.3%), large-cell (22.8%), others (3.5%), not-specified (40.4%). The 57 patients received a total of 64 courses of carboplatin-etoposide: 54 (84.4%) first-line; 9 (15.6%) second-line. Chemotherapy was administered orally (81.2%) or intravenously (18.8%); median number of cycles: 4 (range 1–7). In the first- and second-line settings, median progression-free-survival (PFS) was 5.4 m (95%-CI 3.6–6.9) and 3.4 m (95%-CI 1.6–11.0) and median overall-survival was 7.5 m (95%-CI 6.2–11.5) and 5.8 m (95%-CI 1.6–15.4), respectively. Most common grade 3–4 adverse events in first-second-line were myelotoxicity (29.6%/44.4%), infections (13%/11.1%), venous thromboembolism (11.1%/22.2%); no differences between first-second-line were identified (all P-values > 0.05). Median carboplatin-etoposide dose-intensity was 94.8 and 94.4% in first-second-line, respectively. Line of chemotherapy did not impact PFS (P-value > 0.3). Liver metastases and age were significant in the univariate analysis for PFS and included in the multivariable Cox-regression: presence of liver metastases was the only independent factor related to worse PFS (Hazard Ratio 1.9 (95%-CI 1.1–3.3); P-value 0.03).

Conclusion
Carboplatin-etoposide is associated with survival outcomes in real-life comparable to those reported in current literature. It is an active combination for patients advanced EP-PD-NECs, with a manageable toxicity profile which allows adequate dose-intensity.

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P22
Long-term survival of patients with carcinoid syndrome in clinical trials of telotristat ethyl
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Background
Patients with carcinoid syndrome (CS) in the setting of metastatic neuroendocrine tumours (NETs) experience considerable morbidity and mortality. From the time of diagnosis of metastatic NETs, median survival has been estimated to be approximately 31–75 months. CS is associated with tumoral secretion of serotonin and subsequent debilitating diarrhea, which poses a significant health risk. In previous studies, telotristat ethyl (TE), a tryptophan hydroxylase inhibitor, was effective and well tolerated in treating CS diarrhea. At enrollment, patients in these studies had already survived an average of 6–8 years with metastatic NETs since their initial diagnoses.

Methods
Adverse events reported during treatment with TE were pooled from 2 Phase 2, and 3 Phase 3 clinical trials of TE in patients with CS. The long-term safety of TE was examined, causes of hospitalization and death were reviewed, and an estimate of overall survival was obtained.

Results
A total of 239 patients with CS received treatment with TE in Phase 2 and 3 clinical trials. For these patients, as of the end of 2016, the mean duration of exposure was 1.3 years, and maximum 5.7 years. The leading causes of hospitalization were gastrointestinal disorders and surgical and medical procedures, mostly attributable to the underlying tumor and related treatment. Survival estimates at 1, 2, and 3 years were 93, 88, and 77%, respectively. Nearly all deaths were due to progression or complication of the underlying disease, and none were attributable to TE. There was 1 death in Year 4 and no deaths in Years 5 and 6 of patient follow-up in this data set. The median survival with TE was not reached at the end of the 6-year follow-up period.

Conclusions
Our review of the long-term safety data for TE indicates that patients with CS treated with TE in Phase 2 and 3 studies experienced encouraging survival rates.

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P23
Above-label doses of lanreotide Autogel for the treatment of advanced neuroendocrine tumours (NETs)
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Introduction
High doses/frequency of somatostatin analogues (SSA) are often used to control refractory functional symptoms and/or tumour progression in patients treated with standard doses of SSAs, but there is limited evidence for the efficacy of this strategy.

Methods
Retrospective analysis of 47 NET patients on lanreotide Autogel 120 mg every 3 weeks (as monotherapy). Progression-free survival (PFS) and clinical outcomes were assessed. A 30% change in symptomatology and biomarker levels was considered significant.

Results
Mean age was 62±12 years. The primary tumour site was in the small bowel in 72%, colon/rectum in 13%, pancreas in 11%, lung in 2% and unknown in 2% of cases. Tumour grade was G1 in 49%, G2 (Ki67 2–5%) in 26%, G2 (Ki67 6–20%) in 13%, G3 in 2% (grade unavailable in 10%). Locoregional spread was present in 92% and liver metastases in 85% of patients. Treatment indications were control of functional symptoms (51%), disease progression (38%) and/or increasing biomarkers (11%). Median PFS was 25 months (95% CI 5, 45). In patients with refractory functional symptoms, diarrhoea and flushing improved significantly in 17% and remained stable in 39% of cases. In patients with available biomarkers before and after treatment, CgA and U-5-HIAA levels significantly reduced in 58 and 15% while they remained stable in 16 and 20% of cases, respectively. Treatment was discontinued in 34 cases because of death (8), radiological progression (10), ongoing symptoms (8), a combination of disease progression/functional symptoms (6) and side effects (2). Treatment after discontinuation included PRRT (15), interferon (2), everolimus (2), sunitinib (1), chemotherapy (1), reduction of the administration interval to 2-weekly (1), increase of the lanreotide dose to 180 mg (1), octreotide LAR (1), while one patient was palliated and another returned to standard doses of lanreotide due to side effects on the high frequency regimen.

Conclusions
The use of a shortened interval of lanreotide Autogel administration in patients with radiological and/or symptomatic progression on standard doses of SSA therapy is effective and may prevent or delay the use of other treatments with a more toxic side effect profile.

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P24
Shortened interval of octreotide LAR administration for the treatment of advanced neuroendocrine tumours (NETs)
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Introduction
Escalated doses of octreotide LAR are commonly used to control functional symptoms and/or tumour growth, but there is limited evidence regarding the efficacy of this approach.

Methods
Retrospective analysis of 69 NET patients treated with octreotide LAR 30 mg every 3 weeks (as monotherapy). Progression-free survival (PFS) and clinical outcomes were assessed. A 30% change in symptomatology and biomarker levels was considered significant.

Results
Mean age was 64±11 years. The primary tumour site was in the small bowel in 74% of cases, colon/rectum in 9%, lung 6%, pancreas 4% and unknown in 7%. 41% of tumours were G1, 28% G2 (Ki67 2–5%), 10% G2 (Ki67 6–20%) (grade unavailable in 22%). Loco-regional spread was present in 56% and liver metastases in 55% of cases. Treatment indications were control of functional symptoms (62%), disease progression (33%) and/or increasing biomarkers (10%). Median PFS was 25 months (95% CI 6, 44). Median PFS in patients with radiologically progressive disease was significantly shorter than those with stable disease at initiation of treatment (11 vs 38 months). Diarrhoea and flushing improved significantly in 36 and 14% of patients who received treatment for ongoing functional symptoms, while they remained stable in 46 and 59% of cases, respectively. In patients with available biomarkers before and after treatment, CgA and U-5-HIAA levels reduced significantly in 35 and 29% while they remained stable in 20 and 29% of cases, respectively. Treatment was discontinued in 45 cases because of death (7), disease progression (15), ongoing functional symptoms (9), a combination of radiological progression and ongoing symptomatology (10), symptomatic deterioration and increasing biomarkers (2) and side effects (2). Treatment after discontinuation of the 3-weekly regimen included PRRT (22), interferon (4), sunitinib (1), chemotherapy (1), lanreotide autogel (3), further reduction of the interval of administration to 2-weekly (2), everolimus (2), MIBG therapy (1), external beam radiotherapy (1) and transarterial embolization (1).

Conclusions
A shortened interval of octreotide LAR administration is well-tolerated and can be effectively used as maintenance therapy or as a bridge to other therapies in patients with progressive disease and/or symptomatology.

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P25
Weight change associated with telotristat ethyl in the treatment of carcinoid syndrome
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Background
In the Phase 3 TELESTAR study, the oral tryptophan hydroxylase inhibitor telotristat ethyl (TE) significantly reduced bowel movement (BM) frequency compared with placebo over a 12-week Double-blind Treatment (DBT) period in patients with carcinoid syndrome (CS). Weight loss (WL) has previously been associated with uncontrolled CS and may result in reduced survival, so it is important to examine weight changes in patients with neuroendocrine tumors (NETs).

Methods
We conducted a prespecified analysis of the incidence of weight change of ≥3% at Week 12 in TELESTAR. Patients with metastatic NETs, CS, and ≥4 BMs/day were randomly assigned to receive placebo, TE 250 mg, or TE 500 mg 3×/day (tid) for 12 weeks, in addition to somatostatin analog therapy.

Results
Each group had 45 patients. Mean baseline age was 63.5 years, with 5.8 BMs/day and mean body mass index 24.87 kg/m2. Weight gain (WG) ≥3% at Week 12 was observed in 2/39 (5.1%), 7/41 (17.1%), and 13/40 (32.5%) patients on placebo, TE 250 tid, and TE 500 mg tid, respectively. The Cochran–Armitage test for trend in WG incidence across groups yielded Z=0.28; P=0.6. There were significant differences between survival when patients were stratified by grade or stage (P=0.031). When considering G1 tumours (all stages, n=62), disease stage was not associated with survival (P=0.33). Low-, medium- and high-risk G1 tumours had median survivals of 156, 129 and 62 months, respectively (P=0.005). Similar results were obtained in G1 IIb/IV tumours (171, 143 and 126 months, respectively; P=0.006) and in G1 stage IV tumours (114, 129 and 62 months, respectively; P=0.035).

Conclusions
Predominantly, SB-NET are G1 but most present with nodal/distant metastases, hindering prognostication based purely on grade/stage. Our data demonstrate that multi-parametric assessment may translate into improved prognostication in SB-NET that otherwise would be erroneously predicted to exhibit similar clinical behaviour.

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P27
Supplementation of vitamin D deficiency/insufficiency in patients with GEP-NET using over the counter vitamin D3 preparations
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Vitamin D (vit-D) deficiency is common in patients with gastro-entero-pancreatic neuroendocrine tumours (GEP-NET) and has been linked to reduced survival in these patients. Vit-D status was assessed in 183 patients with GEP-NET, at the time of their first presentation in the ARDEN-NET-Centre; and following simple advice at routine 6-monthly follow-up appointments to increase vit-D intake using over-the-counter vit-D preparations (Calciferol (Vit-D3), 1000–2000 units/day), over a prospective observation period of 24-months. At baseline, 67% of the patients were either vit-D insufficient (31%; 25-OH-vit-D 25–50 nmol/l) or deficient (36%; 25-OH-vit-D <25 nmol/l). 25-OH-vit-D significantly increased from 38.4±4 nmol/l at baseline to 60±6 nmol/l (P<0.0001) and 57±7 nmol/l (P=0.039) after 12 and 24-months, respectively. Percentage of vit-D insufficiency decreased from 66.6% at baseline to 44.9 and 46.2% after 12 and 24 months, respectively. Previous abdominal surgery was the only significant predictor of serum 25-OH-vit-D concentrations in bootstrapped linear regression analyses (P=0.037). In summary: simple advice to increase vit-D intake using over-the-counter preparations significantly improved highly prevalent vit-D deficiency/insufficiency in GEP-NET patients; although, 15% of patients remained deficient and should be considered for additional measures of vit-D replacement.

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P28
Outcomes of radical treatment of NET Liver Metastases: a single tertiary centre 18-year experience
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Background
The presence of liver metastases is a poor prognostic factor in patients with Neuroendocrine tumours (NET). Resection of NET liver metastases (NET mets) has been reported to be associated with good long-term outcomes but must be balanced against the risks of major surgery. Thermal ablation or arterial embolisation offers an alternative to surgery.

Objective
To review the outcomes of radical treatment of NET mets.

Materials and methods
Data was collected retrospectively between 1998 to 2016 of consecutive patients with NET mets who underwent radical treatment (surgical resection, radiofrequency ablation (RFA) and/or trans-arterial embolisation (TAE)) in a single specialist HPB/NET centre.

Results
Fifty-four patients (38.9% male) were included. Median age at treatment was 55 years (range: 14–78). Twenty-one (38.9%) patients had a pancreatic primary NET tumour, 24 (44.4%) in the midgut and 9 (16.7%) in other locations. Forty-four patients had a previous operation for primary tumour resection. Radical therapy consisted of surgical resection in 41 (75.9%), TAE in 5 (9.3%), RFA in 2 (3.7%) and 1 (1.8%) underwent liver transplant. Five (9.3%) patients underwent surgical resection and simultaneous intra-operative RFA. Seventeen (31.5%) patients had low-grade, 21 (38.9%) had intermediate-grade and 8 (14.8%) had high-grade liver metastases and in 8 the grade was not defined. Those with high-grade tumour had a significantly shorter survival. Median follow-up period was 49 months (range: 1–172). Progression occurred in 50% of patients. Median progression-free survival (PFS) was 14.5 months (range: 0–120). Forty of the 54 patients (74.0%) were alive at last follow-up. Median overall survival (OS) was 41 months (range: 0–140).

Conclusion
In this single center experience, liver resection has been the main form of radical therapy for NET mets despite RFA and TAE being available throughout this period. Although progression occurred in 50%, 74% of patients were alive at median follow-up of over 4 years supporting a radical approach for selected patients with NET mets.

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P29
Endoscopic submucosal dissection (ESD) of gastric and rectal neuroendocrine tumours (NETs)
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1Queen Elizabeth Hospital, Birmingham, UK; 2Queen, Birmingham, UK.

Introduction
Duodenal neuroendocrine tumours (d-NETs) comprise about 2% of all NETs. Treatment of d-NETs involves resection of the tumour either by endoscopic or surgical resection. Local resection of the lesion is usually a safer option compared to a more radical pancreatectoduodenectomy. However, inadequate clearance by local resection might result in recurrent disease and reduce the overall survival.

Background
Gastrointestinal (GI) neuroendocrine tumours (NETs) are potentially malignant lesions originating from the enterochromaffin cells of the GI tract. These neoplasms often produce characteristic hormonal syndromes and can cause debilitating symptoms. Endoscopic submucosal dissection (ESD) is a well-established, complex, endoscopic technique, which allows for full resection of the mucosal and submucosal lesions without the need for open surgery.

Methods
We retrospectively reviewed all cases of GI NETs resected by ESD at the Royal Free Hospital between October 2014 and June 2017. Demographic, endoscopic, histopathological and follow-up data were collected and analysed.

Results
Six ESD’s were performed on five patients (all women mean age 57.8 ± 12.1 years). Of the six NETs, there were five located in the stomach (83%) and one in the rectum (17%). All of the gastric NETs were identified as type 1. The main presenting symptoms in patients with gastric NETs were epigastric discomfort, dyspepsia, weight loss, tiredness and gastro-oesophageal reflux. In the case of the rectal NET, the patient presented with similar non-specific abdominal symptoms, but also bleeding per rectum. One patient was identified after a routine workup prior to bariatric surgery. 14-Ga-DOTATATE PET/CT imaging revealed no distant sites of disease in any of the patients. Median lesion diameter was 13 mm (range 4.7–16 mm). Histopathological analysis showed three (50%) well-differentiated grade G1 NETs and three (50%) well-differentiated grade G2 NETs. Using the European Neuroendocrine Tumour Society classification staging system there were four pt1 (67%) and two pt2 (33%) lesions. After ESD, R0 resection was obtained in five lesions (83%) with R1 resection being encountered in one case (17%). No significant adverse events (i.e. perforation, bleeding, sepsis or need for surgery) were observed. Follow-up beyond three months (range: 28.5 months, mean follow-up 21.7 months) showed that all four patients with R0 resections had no evidence of recurrence.

Conclusion
ESD has been demonstrated to be a reliably, minimally invasive therapeutic tool for the resection of gastric and rectal NETs.

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P30
Outcomes of surgical and endoscopic resection of duodenal NETs: a systematic review of the literature
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Introduction
Duodenal neuroendocrine tumours (d-NETs) comprise about 2% of all NETs. Treatment of d-NETs involves resection of the tumour either by endoscopic or surgical resection. Local resection of the lesion is usually a safer option compared to a more radical pancreatectoduodenectomy. However, inadequate clearance by local resection might result in recurrent disease and reduce the overall survival.

Background
The presence of liver metastases is a poor prognostic factor in patients with Neuroendocrine tumours (NET). Resection of NET liver metastases (NET mets) has been reported to be associated with good long-term outcomes but must be balanced against the risks of major surgery. Thermal ablation or arterial embolisation offers an alternative to surgery.

Objective
To review the outcomes of radical treatment of NET mets.

Materials and methods
Data was collected retrospectively between 1998 to 2016 of consecutive patients with NET mets who underwent radical treatment (surgical resection, radiofrequency ablation (RFA) and/or trans-arterial embolisation (TAE)) in a single specialist HPB/NET centre.

Results
Fifty-four patients (38.9% male) were included. Median age at treatment was 55 years (range: 14–78). Twenty-one (38.9%) patients had a pancreatic primary NET tumour, 24 (44.4%) in the midgut and 9 (16.7%) in other locations. Forty-four patients had a previous operation for primary tumour resection. Radical therapy consisted of surgical resection in 41 (75.9%), TAE in 5 (9.3%), RFA in 2 (3.7%) and 1 (1.8%) underwent liver transplant. Five (9.3%) patients underwent surgical resection and simultaneous intra-operative RFA. Seventeen (31.5%) patients had low-grade, 21 (38.9%) had intermediate-grade and 8 (14.8%) had high-grade liver metastases and in 8 the grade was not defined. Those with high-grade tumour had a significantly shorter survival. Median follow-up period was 49 months (range: 1–172). Progression occurred in 50% of patients. Median progression-free survival (PFS) was 14.5 months (range: 0–120). Forty of the 54 patients (74.0%) were alive at last follow-up. Median overall survival (OS) was 41 months (range: 0–140).

Conclusion
In this single center experience, liver resection has been the main form of radical therapy for NET mets despite RFA and TAE being available throughout this period. Although progression occurred in 50%, 74% of patients were alive at median follow-up of over 4 years supporting a radical approach for selected patients with NET mets.

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P31
The utility of the Ki67-Index in predicting pulmonary carcinoid metastasis: a single centre experience
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Background
Pulmonary-NETs are classified in low-grade typical carcinoid (TC), intermediate-grade atypical carcinoid (AC), and high-grade large cell carcinoma (LCNEC) and small cell carcinoma (SCLC). However, the proportion of pulmonary-NETs with small cell carcinoma (SCLC). However, the proportion of pulmonary-NETs with similar histology that behave quite differently is not negligible. Recent studies favour the use of the proliferation marker Ki67.

Objective
To evaluate the utility of Ki67 for predicting metastasis in a cohort of patients with lung-NETs from a single centre.

Methods
We retrospectively reviewed all cases of pulmonary NETs resected by R0 resection status and recurrence rates were the outcomes assessed.

Results
Eight non-randomised retrospective studies with 335 patients were included (LR = 122; PD = 118; ER = 94). PD is associated with higher morbidity compared LR (27/64 vs 10/74; P = 0.002) but is associated with better R0 resection status (3/97 vs 15/97; P = 0.007) and lesser recurrence rates (3/51 vs 6/46; P = 0.21). ER is associated with a higher resection margin positive status when compared to LR group (22/51 vs 14/91; P = 0.0002). ER

Conclusion
Radical surgical resection in the form of PD is associated with better long-term outcomes but with higher post-operative morbidity in patients with dNETs. Larger multi-institutional studies are required to help obtain data to gain consensus based on well-matched cohorts.

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Endocrine Abstracts (2017) Vol 52
Impact of somatostatin analogues on quality of life in patients with neuroendocrine tumours

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Somatostatin analogues (SSAs) are regularly used in the treatment of neuroendocrine tumours (NETs) to control the symptoms of hormonal hypersecretion. Evidence shows that SSAs can reduce tumour progression, and are therefore also being used in patients with non-functioning tumours. As many NETs present with advanced disease curative therapy is often not possible; therefore, assessing the impact of therapy on quality of life (QoL) is vital to patient management. This is particularly true in patients with non-functioning tumours where symptom control is not the primary aim of commencing SSAs.

Aim
To assess whether QoL was being evaluated in patients with NETs being treated with SSAs, and the impact on QoL following treatment with SSAs, comparing symptomatic with asymptomatic patients.

Method
Twenty patients with NETs treated at Queen Elizabeth Hospital Birmingham (QEH) were included: the last 10 symptomatic patients and 10 asymptomatic patients that had been started on SSA therapy and had completed at least 3 months of treatment (as of October 2016). Data was collected about whether validated QoL questionnaires (EORTC QLQ GI.NET21) had been recorded and what the patient management. This is particularly true in patients with non-functioning tumours where symptom control is not the primary aim of commencing SSAs.

Conclusion

The Ki-67-index showed higher values in AC compared to TC and in patients with metastasis. This study suggests that analysis of Ki67-index may be a useful adjunctive measure for predicting metastasis and therefore for initiating early adjuvant multimodal therapy in pulmonary-NETs.

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P33
Double-balloon enteroscopy (DBE) is useful and effective for the diagnosis, assessment and management of small bowel neuroendocrine tumours (SBNETs): a case series from a national tertiary referral centre

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Background
Although small bowel (SB) neuroendocrine tumours (SBNETs) often present as indolent lesions, late diagnosis may result in poor outcomes. Successful management is therefore dependent on early identification. Double-balloon enteroscopy (DBE) enables direct SB mucosal visualisation, sampling and endotherapy. Our aim was to evaluate the role of DBE for early diagnosis and management of SBNETs.

Methods
Retrospective review of all SBNETs diagnosed/evaluated by DBE at our institution (November 2016–July 2017). Demographic, endoscopic, histopathological and follow-up data were collated/analyzed.

Results
A total of five patients were included (mean age: 49 (S.D. ±13.2) years; male/female ratio: 1:5). All patients presented with obscure-overt mid-gut bleeding (OOGIB) (n=3) or iron deficiency anaemia (n=2). A total of six SBNETs were identified in the five patients at DBE. Dedicated SB radiological imaging was performed in four patients and this showed a potential primary lesion in three cases. At DBE, identified lesions were marked with a submucosal tattoo of sterile India ink and histopathology of lesion biopsies was diagnostic of SBNETs in all five patients.

Conclusions
DBE is an essential procedure for early diagnosis and pre-surgical assessment of SBNETs. The role of DBE also extends to localization and marking which may be used to guide minimally-invasive surgical resection.

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P34
Grading systems in gastroenteropancreatic neuroendocrine tumours

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Objective
To compare 3 methods of generating Ki-67% in gastroenteropancreatic neuroendocrine tumours (GEP-NETs).

Methods
Twenty-four slides were used to generate 49 images for analysis. Each image was analysed and 3 different methods were used to calculate Ki-67%.

Results
The comparison of Ki-67% from counting and estimating using the diameter (shortcut method) was strongly positively correlated, whereas the Ki-67% from counting and using ‘immunoratio’ were only weakly positively correlated.

Conclusion
Guidance from The Royal College of Pathologists 2017 states that clinicians must now count 2000 cells from hotspots within the tissue sample to calculate a Ki-67%. The shortcut method gives reasonably accurate results, the online ‘immunoratio’ is less reliable.

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**P35**


Case presentations

Case 1: The index case is a 10 year old girl who presented episodic symptoms of feeling unwell, unexplained headache, seizure, vomiting and dehydrated over a period of 8 months. She was subsequently found to have systemic hypertensive which led to further investigations revealing raised plasma noradrenaline of 32 and 103.7 (NR 0–5 nmol/l). US abdomen suggested bilateral pheochromocytoma but an MIBG showed unilateral left sided increased uptake. She underwent a successful laparoscopic adrenalectomy with clinical and biochemical remission. Case 2: Cascade testing revealed a positive SDHB mutation in her 55 year old paternal uncle. He had been investigated by cardiologist for intermittent chest pain, palpitations and sweating. Investigation showed persistently elevated plasma 3-Methoxytyramine (3-MT) level (561.6/796.5/540.5; NR 0–180 nmol/l) and urine at 6.88/6.51/3.94 (NR 0–2.3 umol/24 hr). MRI head /neck /abdomen and MIBG were unremarkable, and CT showed indeterminate nodule. Subsequent 18F-FDG-PET showed an intensely PET avid lesion. He underwent subsequent resection and histology confirmed an intra-thoracic paraganglioma.

Case 3: The 17 year old daughter of the above patient also had the SDHB mutation but was completely asymptomatic. She had mildly raised urinary metanephrine at 3.04 (NR 0–2.7 mmol/24 hr) and plasma metanephrine at 1539.4 (NR <500 nmol/l) but normal 3-MT levels. MRI thorax/abdomen was normal but 18F-FDG-PET showed an intensely PET avid paraganglioma between the caudate lobe of liver and inferior vena cava.

Discussion

These cases demonstrate paragangliomas can show no or minimally positive symptoms or biochemistry and imaging plays a key role in surveillance. Interestingly all three family members were positive for three different metabolites associated with SDHB mutation. These cases demonstrated very intense uptake on 18F-FDG-PET, highlighting that functional imaging plays an important role in this condition.

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**P36**

Phase I/II open-label trial to assess the safety and preliminary efficacy of $^{177}$Lu-OPS201 as peptide receptor radionuclide therapy in patients with somatostatin receptor-positive, progressive neuroendocrine tumours Guillaume Nicolas1,2, Richard Baum3, Ken Herrmann4,5, Hardeep Singh Mudhar1, Katherine Sears1 & Ian Rennie1,2,6

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**Introduction**

Peptide receptor radionuclide therapy (PRRT) with radiolabelled somatostatin receptor (SSTR) agonists is highly effective and has become an integral part of neuroendocrine tumour (NET) treatment. However, tumour uptake and tumour-to-tissue dose ratios may be higher with radiolabelled SSTR antagonists than agonists. OPS201 (DOTA-JR11) is a very promising next-generation SSTR antagonist selective for SSTR2. (expressed by NETs).

This phase 1/2, international, single-arm, open-label study will evaluate $^{177}$Lu-OPS201 as PRRT in 45 adults with unresectable, SSTR-positive, progressive gastroenteropancreatic (GEP)-NETs, lung NETs, pheochromocytomas and paragangliomas.

Subjects & methods

Patients are recruited at 15 study centres in Australia, Europe, and the US with experience in the use of PRRT (or other radionuclide therapy). The core trial comprises phases A and B: Phase A: six patients receive three cycles of $^{177}$Lu-OPS201 at 4.5 GBq over 24 weeks; a further nine patients receive three cycles of $^{177}$Lu-OPS201 at 4.5 GBq, or an activity not evoking dose-limiting toxicity, dependent on initial safety/dosimetry data. Phase B: 30 patients receive three cycles of $^{177}$Lu-OPS201 at up to 7.4 GBq, dependent on phase-A safety/dosimetry data. In a subsequent long-term follow-up, tumour response (centrally reviewed [RECIST v1.1]) will be assessed using computed tomography/magnetic resonance imaging every 3 months from the end-of-core-trial visit for 2 years, or until progressive disease/death. This core study and long-term follow-up are together expected to last 42–45 months.

**Results**

The primary endpoint is safety and tolerability (based on physical examination, vital signs, electrocardiogram, clinical laboratory measurements, adverse events, dose-limiting toxicities, concomitant medication, pituitary markers and bone marrow aspirate in case of persisting toxicities of grade 3 or more). Secondary endpoints include: biodistribution and pharmacokinetics (molecular uptake, under-curve, terminal half-life); radiation dosimetry; preliminary efficacy (tumour response, progression-free survival), and quality of life. Treatment in phase A is underway.

**Conclusions**

This study will provide important information regarding the safety and efficacy of the radiolabelled SSTR antagonist $^{177}$Lu-OPS201 as PRRT in patients with SSTR-positive, progressive GEP-NETs, lung NETs, pheochromocytomas and paragangliomas (EndoCACT 2018-002867-41; NCT02592707).

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**P37**

Choroidal metastases as a harbinger of metastatic Typical Pulmonary Carcinoid: regression and stability with Lanreotide autogel Edward Foo1, Sachin Salvi1, Alia Munir1, Kurt Sptier Cornish1, Hardeep Singh Mudhar1, Katherine Sears1 & Ian Rennie1,2

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Choroidal metastases were first reported by Perls in 1872. The choroid is the most common ocular site for metastatic disease due to the abundant blood supply. Bilateral lesions are commonly associated with breast carcinoma (40–47%) and unilateral with lung (21–29%). Treatment frequently depends on the patient status but includes observation, systemic chemotherapy, immunotherapy, hormone therapy, radiotherapy, plaque therapy, or photodynamic therapy. Neuroendocrine tumours (NETs) rarely metastasize to the choroid, however, metastasizing lesions from lung NETs have been reported in the literature. We report an asymptomatic 23 year old mother of three, who on a routine optician check was found to have bilateral choroidal lesions 5 years after curative right upper lobeectomy for a Typical Carcinoid of the lung. Clinically these lesions were thought to be either dormant metastatic carcinoid or bilateral uveal melanocytic proliferation. Multimodal imaging available at that time including full body CT and Octreoscan, complemented by full NET biochemistry proved unremarkable, and the patient was closely monitored. At 2 years follow up these lesions increased in size and a choroidal biopsy was performed. Histology confirmed this to be a metastatic NET. Gallium scanning was requested and skeletal lesions suspicious of metastases were revealed. The patient was commenced on a somatostatin analogue (SSA), Lanreotide autogel 120 mg, deep subcutaneous injection every 28 days. Close monitoring revealed possible early regression followed by stabilization of the lesions for 6 months, deeming the SSA treatment successful. MEN 1 gene testing previously proved normal, as were pituitary and bone profiles, and the patient consented to entry into the 100, 000 genome project. Giving the changing paradigm for management of lung NETs, further treatment options for progression would include targeted therapy or PRRT. Previous studies have reported success with SSA and PRRT. Access to gallium scanning for routine NETs is of importance in detecting metastases, which may not be picked up by other modalities. NETs can metastasize to the eyes, which highlights the significance of multidisciplinary collaboration. They need to be closely monitored as an increase in size may necessitate further evaluation and treatment. Choroidal biopsy may be useful in confirming the diagnosis.

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**P38**

Paraneoplastic syndrome or De Novo diagnosis?: Metastatic small bowel neuroendocrine tumour presenting with Giant cell arteritis Ruth Nanda1,2, Ellie Smith1 & Alia Munir1

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Neuroendocrine tumours are rare, with an incidence of 8/100,000 in the UK. They result from excessive proliferation of neuroendocrine cells and are classified based on their site of origin, differentiation and clinical syndrome. Giant cell
A 62 year old lady with a new diagnosis of metastatic carcinoid disease was electively admitted for a right hemicolectomy for a well differentiated small bowel neuroendocrine tumour. This case highlights the need for stringent clinical assessment in this group as successful therapeutic changes maybe indicated.

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P40
Pancratic VIPoma – a diagnostic and symptom control challenge
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A case is reported of a man with stage IV grade 2 pancreatic VIPoma. At diagnosis he had several features which may have expedited the diagnosis including refractory diarrhoea containing undigested foodstuffs, alcohol-related flushing, electrolyte abnormalities and intestinal oedema on imaging. Symptom control was challenging. There was no benefit from creon, loperamide or codeine and escalation to both short and long acting somatostatin analogues was futile. Consistent with a published case report, he gained rapid symptomatic benefit from the tyrosine kinase inhibitor sunitinib. The duration of benefit, however, was less than 6 months. Sunitinib is a symptom control option in somatostatin analogue-refractory VIPoma whilst other more definitive symptom or disease control options are explored. He received one dose of peptide radiomucide therapy but after this he never left hospital due to deteriorating symptoms. Interferon-alpha, known to be of use in carcinoid syndrome, provided some brief symptomatic benefit but unfortunately by this time he was too far along a downward clinical trajectory and he died shortly after.

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P41
Two cases of metastatic neuroendocrine tumours stabilised with somatostatin analogues
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Somatostatin analogues (SSA) have an established role in the medical management of patients with neuroendocrine tumours (NETs). They are effective in the symptomatic treatment of some metastatic NETs and may also provide tumour stabilisation or reduction. We report two patients with disease progression prior to starting SSA and have both benefited from clinical and radiological disease control.

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Phaeochromocytomas are rare neuroendocrine tumours. Prediction of aggressive tumour behaviour remains a major challenge. We report a 68-year-old female who was found to have a locally arising colonic adenocarcinoma on biopsies. Staging also identified a 10.7 cm right adrenal lesion and work-up revealed markedly raised urinary metanephrines and positive MIBG imaging. The MDT decision was to first remove the colonic cancer with appropriate alpha blockade. It was felt that a combined laparoscopic approach would not be appropriate given the size of the adrenal lesion, which might require an open procedure. Histology confirmed a stage III Duke’s C tumour and adjuvant chemotherapy was commenced. Although adrenal surgery had been planned once she completed chemotherapy, she did not tolerate chemotherapy and it had to be discontinued. An open adrenalectomy was finally undertaken. Histology was consistent with a phaeochromocytoma with a PASS score of eight. Two months after adrenal surgery, she reported intermittent tingling and numbness in the left arm with intermittent thoracic back pain. An MRI confirmed a soft tissue mass at T2 extending into the spinal cord. Urinary metanephrines confirmed persistently elevated noradrenaline levels. She underwent bilateral laminectomy followed by spinal radiotherapy. Histology confirmed a metastatic phaeochromocytoma. Post-operative Ga68-DOTATATE PET-CT has since revealed DOTATATE avid lung and mediastinal lymph node metastases. Further systemic treatment of this metastatic phaeochromocytoma has been delayed as a frontal brain lesion has now been identified, which is not DOTATATE avid, and likely represents a low-grade glioma; a craniotomy is planned. Treatment with 177Lu-DOTATATE is being considered following surgery. The management of malignant phaeochromocytomas remains challenging. Radical resection of the primary and metastatic tumours is the treatment of choice. High-dose iodine (131)-MIBG therapy can be used to treat unresectable metastatic disease when MIBG-positive lesions are present. Chemotherapy has been associated with symptomatic improvement and external beam radiation is being used to provide local tumour control or to treat symptoms of local invasion. Peptide receptor radioligand therapy with 177Lu-DOTATATE and/or 90Y-DOTA-TOC has shown encouraging results in small case series and offers an exciting new method in the management of inoperative or metastatic phaeochromocytomas.

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