



**UKI NETS 9th NATIONAL CONFERENCE
1 NOVEMBER 2011**

**ROYAL SOCIETY OF MEDICINE
LONDON**



Abstract Marking Panel

Simon Aylwin, London, UK
John Ayuk, Birmingham, UK
Christos Toumpanakis, London, UK

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Royal Society of Medicine, Tuesday 1 November 2011 Programme

This conference has CPD approval for 6 credits

- 08:30-09:00 Registration
09:00-09:25 Coffee and Poster viewing
- 09:25-09:30 Welcome & Introduction**
Chair of UKINETS Ashley Grossman (Oxford)
- 09:30-10:30 **Session 1 - Dilemmas in the management of NETS: Interactive case discussions**
Chairs: Graeme Poston (Liverpool) & Karim Meeran (London)
- 09:30 Gastric carcinoids: what to do...? Mark Pritchard (Liverpool)
09:50 Refractory hypoglycaemia. Simon Aylwin (London)
10:10 Timing of use of radionuclide therapy in NETs. Val Lewington (London)
- 10:30-11:15 Session 2 - Joydeep Chatterjee Transatlantic Lecture**
Chair: Raj Thakker (London)
- Genetic alterations of the pancreatic neuroendocrine tumours and their implications
Nick Papadopoulos (Baltimore, USA)
- 11:15-11:40 **Coffee**
- 11:40-13:00 **Session 3 - Pathology and tumour markers**
Chairs: Derek Manas (Newcastle Upon Tyne) & Alan Anthony (Leeds)
- 11:40-12:20 Debate: This house believes that there is little point in monitoring serum chromogranin A in patients with NETS
For: Bertram Wiedenmann (Berlin, Germany)
Against: Waljit Dhillon (London)
- 12:20 WHO/ENETS/TNM - Making sense of the pathology report for clinicians
Tim Stephenson (Sheffield)
- 12:50 Novel markers - circulating tumour cells.
Tim Meyer (London)



13:00-14:00 Lunch, poster viewing and exhibition

Judges: John Ayuk (Birmingham)
Christos Toumpanakis (London)
Simon Aylwin (London)

13:00-13:20 AGM

14:00-14:50 Session 4 Nurses session

14:00 Welcome & NET nurse update – nursing implications for new therapies for high grade pancreatic NETs
Philippa Davies (London)

14:10 Sunitinib/Sutent
Linda Pyle (London)

14:40 Everolimus/Afinitor
Robert Goldstein (London)

15:10 Questions

14:00-14:40 Session 4 parallel - Oral communications x 4

Chairs John Ramage (London and Basingstoke) & Aled Rees (Cardiff)

14:00 OC1 - Plasma CART as a prognostic marker for metastatic pheochromocytomas / paragangliomas
Radha Ramachandran, Paul Bech, Kevin.G. Murphy, Zarni Win, Tricia Tan, Bernard Khoo, Martyn Caplin, Mohammad.A. Ghatei, Stephen.R. Bloom, Niamh.M. Martin

14:10 OC2 – The impact of ⁶⁸GA-DOTATOC PET/CT on the multimodal management of patients with neuroendocrine tumours.
Andrea Frilling, Georgios Sotiropoulos, Andreas Bockisch, Massimo Malago

14:20 OC3 - Lutetium 177 Dota Octreotate for advanced GEP NET, well tolerated and effective: outcomes of first UK experience
Nicola Mulholland, Gill Vivian, Muriel Buxton-Thomas, Dorota Dworakowska, Lindsey Devlin, Simon Aylwin, John Ramage

14:30 OC4 - Surgical management of hepatic neuroendocrine metastases - a single centre experience
Rob Jones, Declan Dunne, Stephen Fenwick, Hassan Malik, Graeme Poston



- 14:40-15:30 Session 5 - Imaging and surgical dilemmas in familial paraganglioma**
Chair Nick Reed (Glasgow) & Tom Kurzawinski (London)
- 14:40 What is the best imaging strategy for familial paraganglioma - carriers and affected patients?
Andrea Rockall (London)
- 15:00 When and how to intervene in familial paraganglioma?
Umasuthan Srirangalingam (London)
- 15:20-15:45 Tea & coffee**
- 15:45-16:30 Session 6 - Joydeep Chatterjee European lecture**
Chair: Ashley Grossman (Oxford)
- Discovering the cure for cancer – molecules to medicines in NETs.
Herbie Newell (Newcastle-Upon-Tyne)
- 16:30-17:15 Session 7 - Clinical Trials Update**
Chair: Pippa Corrie (Cambridge)
- 16:30 pNETS – Juan Valle (Manchester)
16:45 Other GI – Graeme Poston (Liverpool)
17:00 First international randomized study in malignant progressive pheochromocytoma and paraganglioma (FIRSTMAPPP)
Angela Rogers (Oxford)
- 17:15-17:20 Closing remarks - Chair UKINETS**
Ashley Grossman (Oxford)
- 17:20-18:30 **Prize giving**
(Wine & cheese will be served)



**ORAL COMMUNICATIONS
SESSION 4**



OC1

**Plasma CART as a prognostic marker for metastaticphaeochromocytomas
/paragangliomas**

Radha Ramachandran^{1,2}, Paul Bech², Kevin.G. Murphy², Zarni Win³, Tricia Tan^{1,2}, Bernard Khoo⁴, Martyn Caplin⁴, Mohammad.A. Ghatei², Stephen.R. Bloom^{1,2}, Niamh.M. Martin^{1,2}

¹Imperial Centre for Endocrinology, London, UK, ²Section of Investigative Medicine,Imperial College, London, UK, ³Department of Imaging, Imperial College, London, UK, ⁴Neuroendocrine Tumour Unit, Royal Free Hospital, London, UK

Malignant phaeochromocytomas/paragangliomas have a poor prognosis. A prognostic marker for this class of tumours would be useful in guiding treatment, but none exists at present. Cocaine- and amphetamine-regulated transcript peptide (CART) is expressed by adrenal medulla chromaffin cells. We assessed plasma CART, CgA and CgB as prognostic markers in phaeochromocytomas/paragangliomas.

Plasma CART, CgA and CgB were measured in phaeochromocytoma (n=15) and paraganglioma (n=25) patients (17 metastatic; 12 of these progressive as per RECIST criteria). The correlation between plasma CART, CgA and CgB levels and tumour burden was examined (n=19; 9 metastatic, 10 non-metastatic).

CgA, CgB and CART concentrations were significantly higher (Mann-Whitney U) in metastatic compared to non-metastatic disease [median, inter-quartile range (pmol/L); CgA 33, 29-47 (non-metastatic) vs. 65, 47-142 (metastatic), $p<0.05$; CgB 83, 55-125 (non-metastatic) vs. 160, 126-205 (metastatic), $p=0.001$; CART 80, 54-130 (non-metastatic) vs. 404, 180-914 (metastatic), $p<0.0001$]. There was no correlation between plasma CART, CgA or CgB and overall tumour burden (multiple linear regression). The combined utility of CART, CgA and CgB was assessed using multiple logistic regression. Only plasma CART remained significantly associated with metastatic disease (AUC 0.83, $p=0.007$) and metastatic progressive disease (AUC 0.78, $p=0.02$).

Lack of correlation with tumour burden and high levels of CART in metastatic progressive disease suggest that plasma CART may predict tumour behavior independent of tumour load. Thus, CART may be a useful prognostic marker in phaeochromocytomas/paragangliomas. A long-term longitudinal prospective study to further evaluate the utility of CART as a prognostic marker is now required.



OC2

THE IMPACT OF ⁶⁸GA-DOTATOC PET/CT ON THE MULTIMODAL MANAGEMENT OF PATIENTS WITH NEUROENDOCRINE TUMORS

Andrea Frilling¹, Georgios Sotiropoulos², Andreas Bockisch³, Massimo Malago⁴

¹Imperial College London, London, UK, ²University Athens, Athens, Greece, ³University Hospital Essen, Essen, Germany, ⁴University Clinic London, London, UK

Background Data

Establishment of the extent and progression of neuroendocrine tumors (NET) is necessary for the decision of which treatment option to choose, however challenging, as morphological imaging is often inadequate to identify the primary tumor and/or to detect small metastatic lesions. The aim of this study was to evaluate the impact of ⁶⁸Ga-DOTATOC PET/CT on the multimodal management of NET.

Methods

In total 52 NET patients, (27 women, 25 men) could be included in the protocol of comparison between ⁶⁸Ga-DOTATOC PET/CT and CT and/or MRI. Each patient presented with either CT and/or MRI and consecutively underwent ⁶⁸Ga-DOTATOC PET/CT.

Results

In all 52 patients, ⁶⁸Ga-DOTATOC PET/CT demonstrated pathologically increased uptake for at least one tumor site, yielding a sensitivity of 100% on a patient basis. In three of 4 patients with unknown primary tumor site, ⁶⁸Ga-DOTATOC PET/CT visualized the primary tumor region not identified on CT and/or MRI. ⁶⁸Ga-DOTATOC PET/CT detected additional hepatic and/or extrahepatic metastases in 22 of the 33 patients diagnosed with hepatic metastases on CT and/or MRI. Of the 15 patients evaluated for liver transplantation, we omitted 7 (46.6%) from further screening due to evidence of metastatic deposits not seen by conventional imaging. Overall, ⁶⁸Ga-DOTATOC PET/CT altered our treatment decision based on CT and/or MRI alone, in 31 of the 52 patients (59.6%).

Conclusions

In this study ⁶⁸Ga-DOTATOC PET/CT proved clearly superior to CT and/or MRI for detection and staging of NET. More important, ⁶⁸Ga-DOTATOC PET/CT impacted our treatment decision in more than every second patient.



OC3

Lutetium 177 DOTA Octreotate for advanced GEP NET, well tolerated and effective: outcomes of first UK experience

Nicola Mulholland, Gill Vivian, Muriel Buxton-Thomas, Dorota Dworakowska, Lindsey Devlin, Simon Aylwin, John Ramage

Kings College Hospital, London, UK

We report our outcomes in use of Lu 177 DOTA Octreotate in advanced gastro entero pancreatic neuroendocrine tumours (GEP NET).

Method:

A retrospective analysis of 26 patients followed for a mean of 21 months (range 3.7 to 51.8) is presented. All patients had inoperable and progressive disease at commencement of treatment. 12/26 had pancreatic primaries, 9/26 had small bowel primaries , 3 unknown and 2 bronchial primaries. Patients received up to 4 cycles of 7.5GBq Lu at intervals ranging between 6 and 16 weeks. 10 patients received 4/4 courses of treatment with mean total dose of 27Gy, 7 received 3/4, 1 received 2/4 and 1 had 1/4 on analysis date. Lysine and Arginine co-infusion was used as a renal protective agent.

Results:

Median PFS was 15 months post treatment, with no significant difference by primary. Median post treatment overall survival for the whole group was 17.3 months respectively, (although patients were only followed for median 18 months). Of the patients who completed intended treatment, complete radiological response was seen in 1/12, partial response 2/12 and stable disease in 8/12 and 1 progression. Symptomatic response was seen in 9 patients. The therapy was well tolerated. Of 12 patients who completed treatment, grade 1 renal toxicity was seen in 1/12 and grade 1 anaemia in 2/12. With our current treatment regime, early mild nausea is not uncommon but vomiting is rare (0/26).

Conclusion:

Lu 177 Octreotate therapy is an effective and well tolerated treatment for advanced GEP NETs.

OC4

Surgical management of hepatic neuroendocrine metastases - a single centre experience

Rob Jones, Declan Dunne, Stephen Fenwick, Hassan Malik, Graeme Poston

Liverpool University, Liverpool, UK

Neuroendocrine cancer is often at an advanced stage by the time it presents, with the majority of patients eventually developing stage 4 disease. Most patients present symptomatically, with hepatic metastases giving rise to systemic carcinoid syndrome. The optimum management for these patients remains unclear. This study reports a single centre experience in the management of stage 4 neuroendocrine disease.

Aim

To assess the impact of surgical resection on symptom control and long term outcome in patients with hepatic neuroendocrine metastases.

Method

A retrospective review of all patients discussed at a neuroendocrine MDT between Jan 1996 and December 2008.

Results

340 patients were reviewed, of whom 150 had stage 4 disease. 117 were treated non-surgically. 33 patients were treated surgically. 14 underwent curative liver resection, whilst 19 underwent cytoreductive surgery (>90% tumour burden) for symptom control. 30-day operative mortality was 0% and 30-day morbidity was 19%. 92% of surgically treated patients reported a complete resolution of symptoms, with a median duration of symptom control of 21 months for those undergoing cytoreductive surgery and 47 months for those undergoing curative surgery. Five year survival was 62% for non-surgical treatment, 74% for cytoreductive surgery and 100% for curative surgery. (Log Rank $p=0.049$). At a median follow up of 66 months, 57% of curative resections had hepatic recurrence.

Conclusions

In selected patients with neuroendocrine liver metastases, hepatic resection improves survival and symptoms. Surgery with curative intent rarely results in cure, with high rates of hepatic recurrence and it therefore seems likely that surgery with curative intent is simply more aggressive cytoreduction. This aggressive cytoreduction gives better symptom control and survival



POSTERS



P001

Neuroendocrine Tumour (NET) Clinic Patient Satisfaction Survey

Andrea Burgess

The Christie NHS Foundation Trust, Manchester, UK

Aim:

To evaluate patient experience in a NET-specific clinic, and current provision of support and information (as per CQUIN indicator and OECl accreditation)

Methodology:

Patients attending the NET clinic were asked to complete a questionnaire during their visit. Questionnaires were returned to the Clinical Audit department for independent analysis; patient anonymity and confidentiality was ensured.

Results:

A total of 104 patients were approached between September/October 2010.

- 84/104 (79%) questionnaires were returned.
- 55% patients knew how to contact the Nurse Clinician.
- 43% of patients on trials knew how to contact the Research Nurse.
- 88% of patients did not have a Key Worker at their referring hospital.
- 57% of patients had received *written* information about their condition and treatment.
- 43% of patients would prefer this information at their first visit.
- 19% of patients were aware of the NET Patient Foundation and
- 29% would be interested in attending a local support group.

Recommended improvements to the service by patients centred on waiting times in the busy NET clinic.

Conclusions:

Results highlighted that the service could be improved for NET patients by the appointment of a dedicated Clinical Nurse Specialist [Key Worker] who would provide information and support in addition to co-ordinating clinic visits and investigations, ensuring efficient throughput and reducing waiting times.

A NET CNS post has subsequently been appointed - the audit will be repeated to measure the effect of this appointment on the patient experience.



P002

Symptomatic Control of Neuroendocrine Tumours with Everolimus

Hannah Bainbridge, Emmanuel Larbi, Gary Middleton

Royal Surrey County Hospital, Guildford, UK

Objective: To evaluate the effect of everolimus on symptomatic control of neuroendocrine tumours.

Methods:

14 patients with metastatic neuroendocrine disease pre-treated with depot octreotide received combination everolimus and octreotide (midgut = 8, PNET = 3, other = 3). Reasons for initiation of everolimus were progressive disease (PD) by Response Evaluation Criteria in Solid Tumours (RECIST) (n= 5), worsening syndromic symptomology (n= 4), and both (n= 5). Symptomatic and objective response and toxicity were evaluated using standard criteria.

Results:

4/5 patients commenced on everolimus for PD without carcinoid symptoms stopped treatment within 2 months due to further PD. 5/9 patients who were syndromic had improvements in symptomology with a symptomatic improvement duration range of 1 month to not reached (patient remains symptom controlled at 11 months), and with a current mean of 5.2 months. Of the 9 patients with symptoms, 4/8 had reduced stool frequency, 2/4 had a reduction in the degree of asthenia, and 3/6 had reduced frequency and severity of flushing. 43% of patients experienced any grade toxicities; 14% grade 1/2 mucositis, 14% grade 3/4 mucositis, one grade 3 rash, one pneumonitis and one grade 3 diarrhoea with hypertriglyceridaemia.

Conclusion:

In this cohort of 14 patients we demonstrated that around 50% of patients with common carcinoid syndrome symptoms resistant to depot octreotide had improvement in these symptoms on institution of everolimus, with meaningful durations of symptom control. Although this data is observational, to our knowledge this represents the largest analysis of carcinoid syndrome control with combined everolimus and octreotide.

P003

How long to continue surveillance in patients following 'curative resection' of primary small bowel tumours?

Rajaventhana Srirajaskanthan¹, Adil Ahmed², John Ramage¹

¹Kings College Hospital, Kings Health Partners, London, UK, ²Bishop Auckland Hospital, County Durham and Darlington, Durham, UK

Introduction

Approximately 50% of patients with small bowel NETs have localised disease at time of presentation; the majority of these patients proceed to surgery for attempted curative resection. The optimal duration of surveillance post 'curative surgical' resection of primary small bowel neuroendocrine tumours (NETs) is not known.

Aims

A retrospective analysis to determine the time to development of metastases following resection of primary tumour +/- mesenteric disease.

Results

104 patients had attempted resection of the primary tumour. Of these 4 cases were unresectable at laparotomy, these cases have been excluded from analysis. There were 4 patients with TNM stage 2 disease, 23 patients with TNM stage 3 disease, 10 patients in whom the staging was not known but had no evidence of residual disease in the initial post-operative period.

36 patients post resection were suitable for analysis. Of these 15 (41.7%) patients have developed recurrent disease. Median period for development of recurrence was 55 months (range 11-606 months).

Conclusion

This study demonstrates approximately 1/3 of patients; develop recurrent disease beyond 5 years (standard duration of follow-up). This study is skewed due to referral bias, in that our institution is a tertiary referral centre and therefore, the majority of patients seen here have recurrent disease. Consequently there is a high percentage of recurrence post resection (41.7%). Consideration of extended follow-up for patients with advanced stage of disease at time of resection may be warranted, however, the cost-effectiveness of this is not known.



P004

Resection of primary tumour improves survival in small bowel neuroendocrine tumours: a single centre experience

Rajaventhana Srirajaskanthan¹, Adil Ahmed², Adrian O'Sullivan¹, Andreas Prachialis¹, John Ramage¹

¹*Kings College Hospital, Kings Health Partners, London, UK,* ²*Bishop Auckland Hospital, County Durham and Darlington, County Durham, UK*

Introduction

Gastroenteropancreatic neuroendocrine tumours are uncommon tumours with an incidence of 0.5-1 per 100 000 population/ year. We report on the survival rates in patients who had the primary tumour resected to see whether primary tumour removal improves outcome.

Aim

To demonstrate if patients who have the primary small bowel NET removed have a longer survival than those in whom the primary is not resected or resectable.

Methods

138 patients with small bowel NETs were identified from the Kings NET database. Primary site: Duodenal 2.1% (3), Jejunal 2.9% (4), ileal 95% (131). A total of 623 patient year's follow-up, with a mean duration of follow-up of 5 years. The median age 61 years (range 24-84).

Results

Of the 138 patients, 100 underwent resection of the primary tumour. Four patients who underwent surgery had un-resectable disease; these patients have been included in the non-resection of primary group. There were no deaths within 30 days post surgery.

Kaplan-Meier survival curves were constructed. There was a significant survival benefit in patients who underwent resection of primary tumour compared to those who did not have the primary resected (120 vs 56 months, $p < 0.005$).

Conclusion

This study demonstrated a marked improvement in survival in patients who underwent resection of the primary tumour compared to those that did not have surgery. The findings may be biased by surgical selection.



P005

Survival and cause of death in patients with small bowel neuroendocrine tumours.

Rajaventhana Srirajaskanthan¹, Adil Ahmed², Parthi Srinivasan¹, Nigel Heaton¹, John Ramage¹

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Introduction

Small bowel neuroendocrine tumours (NETs) have a reported incidence of approximately 0.5-1 per 100 000 population/yr. This study analyses the overall survival for patients with small bowel NET and cause of death over a 25 year from a single centre.

Methods

A total of 138 patients with small bowel NETs were identified from the Kings neuroendocrine database. Primary site: Duodenal 2.1% (3), Jejunal 2.9% (4), ileal 95% (131). A total of 623 patient year's follow-up, with a mean duration of follow-up of 5 years. The median age 61 years (range 24-84).

Results

There were 44 (32.8%) deaths during the follow up period of the study. The 5 year and 10 year survival was 79.5% and 48.5% respectively for all patients independent of stage of disease. There was a significant difference in survival between patients with G1 (Ki67 \leq 2) compared to G2 (Ki67 3-20), $p < 0.05$. The cause of death was related to tumour burden in 50% (22 patients), carcinoid heart disease in 11.3% (5 patients), post intervention (1 surgery, 1 post-embolization) 4.5%, small bowel obstruction or perforation 13.6% (6 patients) and non-tumour related deaths in 24.5% (9) patients.

Of the patients that died the median time to death from diagnosis was 3 years (range 0-14).

Conclusion

The overall 5 year survival is higher than that published in other recent studies. The cause of death demonstrates the non-tumour or disease related deaths account for 24.5% of cases.



P006

Clinical presentation and diagnostic features of small bowel NETs: a single centre experience

Rajaventhana Srirajaskanthan¹, Nicola Mulholland¹, Adil Ahmed², John Ramage¹

¹*Kings College Hospital, Kings Health Partners, London, UK,* ²*Bishop Auckland Hospital, County Durham, UK*

Introduction

We report on the nature of presentation and diagnostic features of a series of patients that presented to a single institution over a 25 year period.

Methods

138 consecutive patients (70 female and 68 males) with small bowel NETs seen in our institution since 1986 were reviewed. 623 years of patient follow-up; mean duration of follow up was 5 years. Median age 61 (range 24-84 years). 130 patients were Caucasian, 7 afro-Caribbean and 1 Asian.

Results

Primary site: duodenal 3 (2.1%) cases, jejunal 4 (2.9%) cases, ileal 131 (95%) of patients.

Clinical features at presentation: carcinoid syndrome in 76 (55%). Non-syndromic symptoms in 62 (45%) patients; of whom 15 (11%) patients were diagnosed co-incidentally. 100 (72.5%) patients had no significant co-morbidity at presentation, 18 patients had a history of IHD, 8 patients had known CCF, COPD in 2 patients and stroke in 3 patients.

Nuclear medicine imaging: n=95 patients. Octreotide was positive in 87 (91.6%) patients with MIBG positive in 43 (72.5%) patients.

At presentation 91 (66%) of patients had distal metastatic disease, 90 hepatic metastases, 4 bone metastases and 2 with lung metastases.

Histology: n=126 patients, of these all were well differentiated NET. None were poorly differentiated NETs. Ki67 or MIB-1 was present in 70 cases of which 16 were G2 and the remainder were G1.

Conclusion

This cohort of patients appears to be a generally healthy population, with 72.5% of patients not having any significant co-morbidity at time of diagnosis.

P007

Does the TNM staging classification predict survival in patients with small bowel neuroendocrine tumours?

Rajaventhana Srirajaskanthan¹, Nikie Jervis¹, Adil Ahmed², Parthi Srinivasan¹, Andreas Prachialis¹, John Ramage¹

¹*Kings College Hospital, Kings Health Partners, London, UK*, ²*Bishop Auckland Hospital, County Durham, UK*

Introduction

Small bowel NETs are regarded as relatively indolent cancers. ENETS have published TNM staging to help stage these tumours. This study aims to demonstrate whether the TNM stage predicts survival in this cohort of patients. Tumour grade was also assessed as well.

Aims

To retrospectively stage patients with known small bowel primary NETs and see whether survival is dependent on stage of disease.

Methods

138 patients with confirmed small bowel NETs were identified from the Kings NET database. Radiological, surgical and histological notes were reviewed to determine stage and grade of disease in patients where possible.

Results

TNM staging and follow-up data was available in 118 cases. Due to low numbers of Stage 2a and 2b tumours these were grouped together as Stage 2 and the same was done for stage 3a and 3b tumours. There were 4 cases with stage 2, 23 cases with Stage 3 and 91 cases with stage 4. Kaplan- Meier plots were constructed these demonstrated a significant difference in survival between patients with different stage of disease (P=0.03). There was no significant difference in survival between stage 2 and stage 3 tumours. There was a significant survival difference between G1 vs. G2 (p=0.049).

Conclusion

There is significant survival difference between Stage IV disease and Stage II and III. There was no significant difference in survival between stages II or III. Low grade tumours Ki67 \leq 2% was associated with better survival than Ki67 3-20. The 5 year survival for patients with stage IV disease was 74%, similar to other studies.

P008

Rare sites of primary Neuroendocrine tumour and metastases

Rajaventhana Srirajaskanthan, Nikie Jervis, John Ramage

Kings College Hospital, Kings Health Partners, London, UK

NETs are known to arise from almost any organ in the body, most commonly from the gastroenteropancreatic system. We present a number of cases below with rare sites of primary tumours and also rare sites of metastatic spread.

Case 1: A patient with previous Kasai operation performed for congenital biliary atresia had developed increasingly cholestatic liver function tests. She underwent a revision of the Kasai operation; at time of surgery a small lesion was identified in the common hepatic duct. Resection was performed and histology demonstrated a 4mm intra-mural well differentiated NET. The mitotic rate was <1 per 10 HPF.

Case 2: A patient with known renal primary NET presents with diplopia. A MRI head demonstrated a small lesion in the lateral rectus muscle of the left eye. He proceeded to have this lesion resected, which demonstrated it to be a well differentiated NET with low mitotic rate and Ki67 <1%.

Case 3: A patient noted a lesion develop on her cheek. A skin resection was performed and this demonstrated a well differentiated NET. She proceeded to have CT and Octreotide imaging which did not demonstrate any other lesions.

Discussion

We identified that bile duct primary NETs have been reported previously, though are exceedingly rare. Renal NET are relatively uncommon, there has never been a reported case of a renal NET metastasizing to the orbit. Skin metastases are well documented in the literature; however, this is the first report of a primary presentation of a NET with skin metastases.

P009

NEW PARAGANGLIOMA MUTATION: DISCUSSING ITS CLINICAL SIGNIFICANCE AND FOLLOW-UP

Carmen Tenorio Jimenez, Hyma Rachabattula, Paul Carroll, [Barbara McGowan](#)

Guy's and St Thomas' NHS Foundation Trust, London, UK

Introduction

Familial pheochromocytomas, inherited as an autosomal dominant trait, can be associated with constitutional mutations in several genes. Individuals carrying an SDHD or SDHB mutation may be at risk from both pheochromocytoma and head and neck paraganglioma.

Case Presentation

A 30 year-old Caribbean lady was referred to the endocrine department for elevated urinary catecholamines whilst she was being investigated by the neurologists due to continuous headaches. There were no palpitations or sweating episodes. On examination, she was normotensive. An abdominal CT scan showed an extra-adrenal solitary heterogeneously enhancing mass located within the left hypochondrium retroperitoneally. The lesion was shown to be MIBG-avid.

Surgery

A laparoscopic/mini open resection of extra adrenal left mass was performed. The normal left adrenal gland was left in situ. Pathologic analysis of the tumour showed a mass measuring 7.5 x 7 x 3cm with areas of necrosis and haemorrhage. The histology was that of pheochromocytoma. The margins appeared negative for tumour.

Genetics

The patient was found to carry a **p.Ala3Gly variant at codon 3 in exon 1 of the SDHB gene.**

Discussion

Mutations of genes encoding *SDHB*, *SDHD*, *SDH5* and rarely *SDHC* are the most recently identified genetic causes of paraganglioma. Mutations of these genes are associated with relatively high rates of extra-adrenal tumours, but *SDHB* mutations appear to be associated with more aggressive tumour behaviour and a higher rate of malignancy (66-83%). Patients with these mutations may also present with head and neck paragangliomas without biochemical evidence or signs and symptoms of a catecholamine-producing tumour. The change here reported does not appear in the current mutation databases as either a disease causing mutation or a neutral variant. Unfortunately the significance of this change is unknown. To date, her 6-year periodic follow-up has not shown any recurrence or associated tumours.

P010

CARNEY STRATAKIS SYNDROME IN A PATIENT WITH SDHD MUTATION

Carmen Tenorio Jimenez, Tomas Agustsson, Paul Carroll, [Barbara McGowan](#)

Guy's and St Thomas' NHS Foundation Trust, London, UK

Introduction

Carney Stratakis syndrome (CSS) is an association of familial paraganglioma and gastric stromal sarcoma tumour (GIST). It is considered to be distinct from Carney's triad as CSS is dominantly inherited and not associated with pulmonary chondroma. Germline mutations in SDHB, SDHC or SDHD have been reported in 8 out of 11 patients from 7 unrelated families diagnosed with CSS.

Case presentation

A 24-year-old gentleman presented with a hoarse voice and a mass in the left neck. On examination, he was hypertensive, BP of 166/112. He had a left-sided vocal cord palsy and some incipient weakness in his left trapezius. A 2 cm mass was palpable in the left carotid triangle. A neck CT and MRI showed a left-sided carotid body tumour and right-sided glomus vagale tumour that had eroded into the temporal bone. Urinary catecholamines were normal. Carotid angiography, MIBG and PET scan confirmed the diagnosis. Imaging revealed further paraganglia in the left side of his abdomen. There was a family history of paragangliomas in his father and paternal aunt.

Surgery

The patient underwent an uneventful laparotomy. At surgery, 3 para-aortic lesions (paragangliomas) were identified and excised. He received gamma knife radiosurgery to his right cervical carotid glomus tumour and underwent excision of his left carotid body tumour and glomus vagale tumour.

Genetics

Gene analysis revealed a germ line nonsense mutation (p.Trp5X, C.14G>A) in exon 1 of the gene that encodes for SDHD.

Follow-up

At age 29, a follow-up abdominal MRI showed a small lesion arising from the gastric antral wall. He underwent a laparoscopic resection. Histopathological evaluation revealed 15mm nodular tumour consistent with a GIST.

Discussion

To our knowledge, abdominal paragangliomas associated with GISTs have been associated uniquely with SDHC mutations. We have reported a case of multiple paragangliomas, including abdominal tumours, and GIST in a patient with a SDHD mutation.

P011

Insulinoma presenting in a patient with a diabetes glucose value on 2 hour Oral glucose tolerance testing

Ian Seetho, Nigel Sturrock

Nottingham University Hospitals NHS Trust, Nottingham, UK

A 48 year old Caucasian woman was seen in clinic with symptoms that were suspicious of an insulinoma. Clinical examination was normal and she had a normal body mass index. We noted an oral glucose tolerance test result that had been performed three months previously [Glucose at 0mins: 4.6mmol/L, 120mins: 11.3mmol/L].

Repeat fasting glucose values ranged between 1.5 and 1.7 mmol/L, associated with raised insulin 8.2 and 10.8mU/L and C-peptide concentrations 758 to 864pmol/L respectively. An MRI scan of her abdomen showed a 6.2cm mass in the tail of her pancreas.

She had a laparoscopic distal pancreatectomy and the histology confirmed that she had an insulinoma. Her blood glucoses post-surgery were all within normal limits. An oral glucose tolerance test a few weeks later excluded diabetes (0 mins glucose: 5.2mmol/L; 2 hour glucose: 7.5mmol/L).

An insulinoma presenting with a diabetes range blood glucose value during an oral glucose tolerance test has to our knowledge never been reported before. The high glucose reading at 2 hours may have been due to an initial impaired ability to respond to the large glucose load because of the presence of the islet cell tumour. With the subsequent onset of hyperinsulinaemia; an increased rate of glucose assimilation and a decreased rate of gluconeogenesis due to immense insulin secretion, this would eventually lead to subsequent low blood glucose levels.

P012

MANAGEMENT OF PARAGANGLIOMA IN PREGNANCY

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INTRODUCTION:

A catecholamine secreting Paraganglioma is rarely observed during pregnancy. Pregnancy prognosis is influenced on accurate diagnosis and multidisciplinary management. We report the management of a Paraganglioma in a 12 week pregnant woman.

CASE PRESENTATION:

A 33 year old lady from Russia who was 12 weeks pregnant at booking into her second pregnancy presented with severe hypertension. She was on antihypertensives up until 6 months prior to the recent pregnancy. She had associated symptoms of palpitations, sweating, nausea and infrequent headaches for the last 6 months. The BP was 180/70 mmHg and the rest of the examination was unremarkable. She was initiated on phenoxybenzamine and labetalol in titrated doses. 24 hr urinary catecholamines were significantly elevated (5 times the upper normal limit). She had normal cortisol, thyroid function, calcium and glucose levels. The MRI abdomen demonstrated a 7.5x7.5cm extra adrenal right paraganglioma with distortion of the inferior vena cava. Surgical resection of paraganglioma was performed at 20 weeks of gestation. Histological examination had confirmed a complete resection with PASS 1/20. She made an excellent recovery. The BP improved and antihypertensives were stopped. 24 hr urine catecholamines normalized. She has delivered a baby and SDH analysis is awaited.

CONCLUSION:

Our case report of paraganglioma in a 12 week pregnant lady highlights the importance of identification of paraganglioma in pregnancy. Although there is no consensus on the optimal management of paraganglioma in pregnancy, early initiation of alpha blockade and timing of the surgical intervention is critical in improving the pregnancy outcome.



P013

International Validation of EORTC GINET-21 Quality of Life scoring system in neuroendocrine tumours.

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Patients were recruited into this multi-international centre study from January 2006 to January 2010. Primary sites included were: any gut primary with metastases, lung with liver/abdominal metastases or pancreas with or without metastases and all with or without hormone secretion. Expected survival of at least 3 months and a planned treatment for NET were requirements.

Patients completed the EORTC QLQ-C30(version 3.0) and the QLQ-G.I.NET21 at all assessment points. The QLQ-G.I.NET21 contains 21 items organized into 5 scales- endocrine symptoms(3 items), G.I.symptoms(5 items), treatment related symptoms (3 items), social function(3 items), and disease related worries(3 items) and 4 single items- pain, body image, communication and sexuality. Patients were allocated into 2 groups depending on the treatment they received. Group 1 included somatostatin analogues or interferon therapy where QoL assessments were done before and during a long-term continuous treatment. Group 2 included all other active therapies. The HRQOL assessments took place before commencement of treatment (baseline) and follow-ups at 3 months and 6 months after treatment. Test retest reliability was assessed on 48 stable patients who at 2 weeks after 6 month assessment. In total, 661 questionnaires were available for the analyses.

Results: Cronbach's alpha was >0.70 in all scales at baseline (except treatment-related and social functioning scales which achieved this at time point3). Intra-class correlation was >0.75 for all scales and single items. All items had correlations above 0.40 with their own scales (0.58 to 0.91), supporting item convergent validity. Item discriminant validity was confirmed as all new module scales had correlations of less than 0.70 with each other. Endocrine symptoms; G.I. Symptoms; Social function; disease related worries showed significant changes over time. The GINET-21 is a useful, valid and responsive tool for assessing QoL in NET's when used with the QLQ-C30 questionnaire.

P015

Metastatic Neuroendocrine Carcinoma:

How feasible is the laparoscopic approach to liver resections?

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Background:

The feasibility and efficacy of laparoscopic liver resection (LLR) are well documented, but there are no reports describing results in a dedicated cohort of patients with neuroendocrine tumours (NETs). We describe our experience of LLR for NETs as part of a multimodal cytoreductive approach in a single centre NET tertiary referral unit.

Aim:

To evaluate the feasibility of the laparoscopic approach to liver resections in metastatic NETs.

Methods:

All patients assessed for metastatic intra-abdominal NETs from April 2005-August 2011 were prospectively registered on a database; patients undergoing LLR were identified. Demographic, peri-operative and survival data were analysed using SPSS version 12.0. Severity of operative and post-operative morbidity was graded using the Clavien system.

Results:

The NET MDT assessed 204 patients. 64 patients had liver resections. 25 patients had 27 LLR; 11 females, 14 males, median age 62.5 years (45–78). 7 major resections, 12 multiple metastectomies and 8 solitary metastectomies were performed. Median post-operative stay was 4 days (0–12).

4 patients underwent LLR with curative intent, 21 patients with palliative intent. 2 patients died of recurrence after median 20.5 months (16-25), 23 are alive after median 16 months (2-48) follow-up.

Two patients (7.4%) had post-operative complications (Grade IIa and III morbidity). There was no peri-operative mortality, with no cases of carcinoid crisis, bile leak or port site metastases.

Conclusion:

This is the first series to demonstrate that LLR for neuroendocrine metastases can be performed with low morbidity and mortality by experienced surgeons operating in a tertiary referral unit.



P016

A diagnostic performance assessment of the Cisbio chromogranin A ELISA assay.

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Introduction:

Chromogranin A (CgA) is the most practical and useful general tumour marker in patients with neuroendocrine tumours (NETs). Accurate measurement of CgA is complex as processing of CgA varies according to neuroendocrine cells/tissue. Several commercial assays for the measurement of plasma CgA are available.

Method:

A diagnostic two-gate case-control study was conducted to assess the diagnostic performance of the Cisbio Chromoa™ assay. 65 case samples were collected from patients attending the neuroendocrine out-patients clinic between March 2010-11. 38 control samples were collected from healthy volunteers who were not being prescribed proton pump inhibitors at time of sampling. Plasma samples from a sub-group of 26 patients with other cancers (non-NET), including lung and breast cancer were collected to assess the specificity of the CgA assay. Samples were assayed in batch to exclude inter-assay imprecision. Diagnostic performance was assessed by receiver operating characteristic (ROC) curve analyses.

Results:

ROC curve analysis indicated a diagnostic cut-off at 117 ng/mL gave a specificity of 97% with corresponding sensitivity at 80%. The overall test accuracy was expressed as area under the curve (AUC) = 0.90. Using a control sub-group of non-NET cancer patients to generate a ROC curve lowered the AUC value for the assay to 0.70 and at the diagnostic cut-off lowered the specificity to 62%.

Conclusion:

The assay reference range was higher than that quoted by the manufacturer. The assay performed well in patients with diagnosed NETs. However, the diagnostic performance of the assay was compromised when comparing NETs with other cancer groups.



P018

An Acute Shower of Circulating Tumour Cells following Transarterial Embolisation (TAE)

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Introduction:

Shedding of tumour cells following transarterial-embolisation (TAE) in NETs has not previously been demonstrated.

Aim:

We have analysed changes in circulating tumour cells (CTCs) and Cell Free DNA (cfDNA) in patients with Neuroendocrine Tumours (NETs) undergoing TAE for hepatic metastasis

Methods:

Twelve patients were studied. Blood was analysed for CTCs and cfDNA at baseline and post-procedure on days 1, 2, 3, 4 and week 6. CTCs were enumerated using the CellSearch system as previously described. cfDNA was extracted from plasma using a Qiagen mini-kit (Qiagen,UK) and quantified with a High Sensitivity Chip on an Agilent Bioanalyser 2100. As a control, 5 additional patients with metastatic NETs had samples taken before and after PRRT (2),surgery (2), RFA (1).

Results:

10/12 undergoing TAE had CTCs at baseline (range 0-147). All 12 had an increase in CTCs at day 1 post-TAE (median increase 695% over baseline, range 156-3100%). Increases in cfDNA corresponded to CTC increases but lagged by one day. No patient undergoing other treatments had any increase in CTCs.

After a median FU of 4 months, 3 patients have died (OS 2.5, 1.9, 0.6 months), 2 of which had the smallest post-TAE CTC increases (by 5 and 7 respectively). CTCs recovered to below baseline in all but 2/12 patients (these 2 patients died).

Conclusion:

We demonstrate an acute 'shower' of CTCs and cfDNA following TAE. Better survival following TAE may be predicted by a reduction of CTCs below baseline but further follow-up in a larger cohort of patients is required.



P019

Development and validation of the world-wide first automated Chromogranin A assay, using BRAHMS KRYPTOR instrumentation

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Chromogranin A (CGA), a member of granin and secretin protein family, is widely expressed by neuroendocrine tissues and is recognized as a highly reliable neuroendocrine tumour marker. We developed a new homogeneous CGA assay for the fully automated BRAHMS KRYPTOR instruments. The aim of this study was to evaluate the analytical performances of this assay.

Our sandwich assay uses the sensitive Time Resolved Amplified Cryptate Emission technology, based on nonradiative energy transfer between 2 fluorophores, europium cryptate and XL665. Sample volume and incubation time are only 8 µl and 29 minutes.

The direct measuring range of the assay is 0-3000 ng/mL and samples up to 1000000 ng/mL can be measured with automatic out-of-range detection and dilution. The linearity was checked with recoveries being 81-116%. Assay imprecision was evaluated following CLSI EP5-A2 (3 reagent lots, 2 instruments, 20 days). The intra and inter-assay coefficients of variation, respectively, were 1.8% and 5.9% at 102 ng/mL and 1.1% and 7.1% at 2255 ng/mL. The limits of detection and quantitation were 6.2 and 10 ng/mL, respectively. The assay was compared to the widely used manual CGA assay from Cisbio International (n=331, range 7.7 – 31143 ng/mL). The concordance is excellent with spearman correlation coefficient at 0.99, slope at 1.03 and intercept at -8.8 by Passing-Bablok regression fit.

The BRAHMS CGA KRYPTOR assay is the first automated CGA assay which brings major improvement for clinical laboratory support of neuroendocrine tumor management.

P020

Effective Use of Pre-Operative Etomidate in Rapidly Progressive Severe Cushing's Syndrome

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Rapidly progressive Cushing's Syndrome is associated with a poor prognosis and may be challenging to control with conventional agents. For example, the efficacy of Metyrapone or Ketoconazole is frequently limited by poor tolerability. Prompt surgical intervention, with the aim of curing or debulking the underlying disease typically offers prognostic benefit whilst accepting that operative mortality is increased by the consequences of glucocorticoid excess; increased infection risk, tissue friability and poor wound healing.

Etomidate, an intravenous anaesthetic agent, is a reversible inhibitor of the adrenocortical enzyme 11-beta-hydroxylase. We describe its role in stabilising two patients with florid uncontrolled Cushing's syndrome. A 39 year old female and a 30 year old male presented concurrently with rapidly progressive Cushing's syndrome. Radiological and biochemical investigations revealed a likely pancreatic neuroendocrine primary tumour and an adrenocortical carcinoma respectively. Both individuals deteriorated rapidly whilst surgery was being planned with average cortisol levels of 944nmol/l and 1062nmol/l respectively on maximal tolerated conventional therapies. Excellent pre-operative control was achieved by infusing etomidate on the intensive care unit with mean cortisol profiles of 224nmol/l and 382nmol/l respectively.

Discussion:

We report two patients with rapidly progressive, life-threatening Cushing's syndrome in whom the elective pre-operative use of intravenous etomidate was safe, effective, well tolerated and secured good medium-term post-operative outcomes. Given the associated expense, we propose that within specialist neuroendocrine centres, with close ICU liaison and careful case selection through an experienced MDT, this technique has validity in a small cohort of highly complex Cushing's patients uncontrolled by conventional therapies.

P021

A case report of extraocular metastases four years post-resection of primary renal carcinoid arising from crossed-fused renal ectopia

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The association of malignancy with fusion anomalies of the kidney such as horseshoe kidney and crossed-fused renal ectopia is very rare. Primary renal carcinoid tumour is an uncommon malignancy and metastases have been reported in isolated cases involving the lymph nodes, liver, lung and bone with isolated case reports of extraocular metastases.

A 34-year-old man presented with loin pain, vomiting and weight loss. Computed tomography (CT) of the abdomen revealed a crossed-fused kidney. He underwent left-side nephrectomy and right-side partial nephrectomy with paraaortic lymph node dissection. The postoperative histology showed a completely resected pT3N3MX atypical carcinoid tumour. Four years later he presented with right eye swelling, orbital pain and diplopia. On examination he had axial proptosis and reduced light perception. Both CT and MRI demonstrated enlargement of the right lateral rectus muscle in a fusiform manner displacing the optic nerve. He underwent a right lateral orbitotomy with debulking. Histology was in keeping with carcinoid metastases. Six months later a CT scan of the abdomen showed a new pelvic soft tissue mass and an MRI of the orbits showed a left-side extraconal mass adjacent to the left lateral rectus muscle; both areas corresponded to increased uptake on octreotide scanning. He is currently awaiting further surgical management.

Although carcinoid tumours appear to have a propensity to metastasise to the extraocular muscles, to our knowledge this is the first case report of such metastases from a carcinoid tumour arising from crossed-fused renal ectopia.

P022

Insulinoma and phaeochromocytoma in neurofibromatosis type-1.

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A 75 year-old female with neurofibromatosis type-1 (NF-1) presented with a reduced level of consciousness and hypoglycaemia. She described a history of recurrent episodes of visual disturbance followed by collapse occurring on fasting and occasionally resolving on eating. The patient was hypertensive.

A 72-hour fast confirmed endogenous hyperinsulinaemic hypoglycaemia. Laboratory glucose fell to 2.1mmol/L with insulin 82pmol/L (18-77), pro-insulin 79pmol/L (<10) and c-peptide 0.81nmol/L (0.27-1.28). 24 hour urinary metanephrines collection revealed an elevated metadrenaline level of 4.31umol/24hr (<1.40).

MRI scan showed a lesion at the junction of the head and body of pancreas and bilateral adrenal nodules. Endoscopic ultrasound showed a hypoechoic lesion in the body of pancreas. Selective pancreatic arteriography with calcium stimulation and hepatic venous sampling showed a 2-fold increase in hepatic venous insulin concentration following injection into the inferior pancreatico-duodenal artery. MIBG scan showed a single focus of avid MIBG uptake in one of the right adrenal nodules.

Diazoxide failed to control the hypoglycaemia and prednisolone was added. Alpha blockade was initiated. Having localised the insulinoma, the patient is awaiting pancreatic surgery and right adrenalectomy for the phaeochromocytoma.

Insulinomas are rarely seen in NF-1, unlike phaeochromocytomas, paragangliomas and duodenal somatostatinomas. We report the fourth case in the literature of an insulinoma in NF-1. Clinicians should be aware of the possibility of insulinomas in patients with NF-1. Conversely, however, it is unlikely that a patient with an apparently sporadic insulinoma harbours an NF-1 germline mutation as the clinical phenotype of NF-1 is usually obvious.



P023

The First Neuroendocrine Tumour Methylome Using Methylation Specific Immunoprecipitation Followed By Second Generation Sequencing – Medip-Seq.

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Introduction:

The study of DNA methylation at cytosine-guanine (CpG) sites is of particular importance in cancer as causal involvement has been demonstrated. Recently, the first cancer methylomes have been produced which identified differential methylation at CpG island-shores (2kb upstream of CpG islands) to be of particular importance in the tumourigenic process. This is the first “methylome” to be produced in NETs using second generation sequencing.

Methods:

Nine fresh frozen (FF) sporadic pancreatic NET (PNET) liver metastases (3 low, 3 intermediate and 3 high grade) and two normal pancreatic paraffin embedded (FFPE) tissue samples underwent whole-genome CpG methylation specific immunoprecipitation followed by second generation sequencing on the Illumina GAIIx sequencer (MeDIP-seq). This approach enables up to 75% coverage of the ~28 million CpGs present in the human genome. The MeDIP-seq data were processed using our novel analysis pipeline MeDUSA. MeDUSA performs a full analysis of MeDIP-seq data, including sequence alignment, quality control (QC), and determination and annotation of differentially methylated regions (DMRs).

Results:

Between 21 and 50 million unique reads were mapped per sample. Using an FDR of 0.01 (1%), DMRs (for hyper and hypomethylation) were identified between normal pancreatic tissue and low (3546), intermediate (17542) and high (11219) grade pancreatic NETs and also between low and intermediate (5021), low and high (5292) and intermediate and high (6815) grade pancreatic NETs. A marked difference in the proportion of hypermethylated DMRs occurring in CpG islands and CpG island-shores was observed between low, intermediate and high grade tumours. An increase in the number of hypomethylated DMRs was observed in repeat elements such as long and short interspersed nuclear elements suggesting global hypomethylation, this is likely to contribute to the genomic instability observed in pancreatic NETs.

Conclusions:

This is the first MeDIP-seq analysis to be performed in NETs. Initial data analysis has highlighted significant differences in methylation at CpG islands – and for the first time at CpG island-shores between different grades of PNET. Pathway analysis and DMR validation is in progress, this will improve understanding of PNET pathogenesis and identify novel biomarkers specific to PNET tumour grade.

P024

A Pheochromocytoma as a source of Ectopic ACTH – A Severe Management Challenge

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Case:

A 49 yr old lady presented with new onset hypertension and oedema. Investigations revealed ACTH-driven endogenous hypercortisolaemia and raised plasma and urine catecholamines. Imaging revealed a necrotic left adrenal mass on abdominal CT scanning, with ring-enhancement on ¹²³I-MIBG scanning. She was diagnosed with Cushing's syndrome from ectopic ACTH secondary to an adrenal pheochromocytoma. During preoperative adrenergic blockade (phenoxybenzamine + propranolol) she developed severe hypertension, acute pulmonary embolism and lung consolidation. This led rapidly to respiratory failure needing 3 days of mechanical ventilation in ITU. She responded to antibiotic therapy plus adrenolytic therapy with metyrapone and ketoconazole, and then proceeded to uneventful laparoscopic left adrenalectomy.

The tumour was a typical pheochromocytoma which also stained immunohistochemically for ACTH. Biochemical resolution of her hypercortisolaemia was rapid and she now shows resolution of her clinical syndromes, and normal metanephrine excretion and cortisol dynamics.

Review:

Review of literature reveals that a pheochromocytoma is the source of the ACTH in only 4% of patients with ectopic ACTH secretion. Of the 24 reported cases, the median age was 45.5 (25 – 74) years, with a high female: male ratio and a predominance of left-sided adrenal lesions. There was only one malignant lesion and one associated with MEN1. The clinical course observed in our patient is typical of similar cases reported and highlights the dual problems of managing hypercortisolaemia and increased catecholamines while unwell prior to surgery.

Conclusion:

Pheochromocytomas can be an important source of ectopic ACTH and their successful management requires close collaboration between physicians, intensivists, anaesthetists and surgeons.

P025

Risk Of Adrenocortical Carcinoma In Cortical Adrenal Tumours Larger Than 8 Cm

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Background:

The incidence of adrenocortical cancers (ACC) in patients with adrenal tumours increases in parallel with the maximum diameter.

Methods:

Retrospective review of patients undergoing adrenal surgery in a large University centre.

Results:

Between 2000-2010, 220 patients (130F:90M, age 17-87 years) underwent adrenalectomy for pheochromocytomas (n=90), functional (n=64) and non-functional (n=56) cortical tumours and metastases (n=7).

Mean tumour diameter for cortical adrenal tumours (n=120) was 7.2±5.7 cm (range 0.6-22cm). Tumours >8 cm were diagnosed in 27 (12%) patients of whom only one had evidence of metastatic disease (stage IV ACC) and 26 had local disease (Table). Laparoscopic adrenalectomy was performed in six patients and open adrenalectomy on 20 patients, 14 of which had simultaneous nephrectomy (n=8), splenectomy (n=4) or distal pancreatectomy (n=2). During mean follow-up of 35 months (range 6-93 months) the overall mortality in patients with tumours > 8 cm in comparison to those with tumours<8cm (37% vs. 9%). Adjuvant Mitotane chemotherapy was not offered routinely to patients with stage II disease but this had no negative impact on their outcome (Table).

Cortical tumours>8cm	Mitotane treatment	5-yrs disease-free survival	5-yrs overall survival	p
Metastatic disease (stage IV)	YES n=9, NO n=1	30%	60%	P=0.0009
Local invasion (stage III)	YES n=0, NO n=1	0%	0%	
Limited disease (stage II)	YES n=4, NO n=12	50%	50%	NS

Conclusion:

Size >8 cm is a predictor of poor outcome in patients with stage III-IV disease but lacks specificity in defining the diagnosis of ACC in the absence of local invasion or metastatic disease.

P026

Comparison of performance of 68-Gallium DOTA-octreotate scanning versus 123-Iodine MIBG in the detection of pheochromocytoma and paraganglioma disease.

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Objective:

To compare the sensitivity of 68-Ga DOTATATE scanning versus 123-I MIBG in patients with pheochromocytoma (PCC) and paraganglioma (PGL).

Methods:

A retrospective analysis of patients with PCC/PGL who underwent both 68-Ga DOTATATE PET/CT and 123-I MIBG SPECT, within 6 months of each other. All images were independently analysed by a blinded nuclear medicine radiologist.

Results:

15 patients were identified. 10/15 cases (66%) had a familial PGL syndrome (7 SDH-B, 2 SDH-D, 1 c-Ret), of which 9/10 (90%) presented with extra-adrenal disease. In a per patient analysis, 8 cases had concordant 68-Ga DOTATATE and 123-I MIBG scans. Five cases had positive 68-Ga DOTATATE imaging, but had negative MIBG imaging. Two cases had positive 123-I MIBG with negative 68-Ga DOTATATE (further analysis of these 2 cases suggests that the regions of 123-I MIBG uptake were false positives). Analysis by anatomical distribution of uptake showed that 68-Ga DOTATATE was more sensitive than 123-I MIBG in detecting metastatic disease, particularly in four cases of head and neck PGL, which were positive on 68-Ga DOTATATE imaging, but not with 123-I MIBG. Per lesion analysis showed 68-Ga DOTATATE detected more lesions in all anatomical areas compared to 123-I MIBG, particularly with regards to bony metastases.

Conclusions:

68-Ga DOTATATE imaging should be considered as first line in patients with familial PGL syndromes, particularly those at high risk of head and neck disease. In patients with high clinical suspicion of disease but negative MIBG imaging, 68-Ga DOTATATE imaging may be valuable.

P027

Comparison of Indium-octreotide vs Indium-dotatate scintigraphy in the detection of neuroendocrine tumours

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Introduction:

In the absence of Gallium Dotatate, we routinely use In111 Dotatate to characterise neuroendocrine tumours pre and post targeted radionuclide therapy. A review of the clinical usefulness of these scans was performed especially in the context of diagnostic In111 octreotide scans.

Methods:

Between May 2008 and May 2011, sixty-two patients underwent both Indium-octreotide and Indium-dotatate scans. Only the pre-therapy scans were compared for this analysis. Findings were compared by counting the number of lesions identified on each scan. All cases were reviewed to determine whether the Indium-dotatate findings resulted in any alteration in management, in terms of suitability for peptide receptor therapy.

Results:

Of the 62 patients, 28 had evidence of more lesions on dotatate scans as compared to the octreotide scans. 173 additional lesions were identified (average of 6 lesions per patient). In 16 patients, counting of lesions was not possible due to diffuse uptake. 13 patients had the same number of lesions on both types of scans. In 5 patients, more lesions were seen on the octreotide scans as compared to the dotatate scan. 12 additional lesions were identified (average of 2.4 lesions per patient). Following dotatate scintigraphy, 37 patients were deemed suitable for therapy with Y90 and 17 with Lu177. 8 cases went for further MDT discussion and different treatment strategies.

Conclusion:

Indium-dotatate scintigraphy is more sensitive than octreotide scintigraphy in the detection of neuroendocrine tumours. It is helpful in identifying additional lesions and may alter patient management. This technique is useful in units without access to Gallium dotatate imaging.

P029

How aggressively should we manage hyperparathyroidism with very small multiple islet-cell tumours and gastrin excess in MEN-1?

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This 30 year old Caucasian male presented with 4 years history of severe dyspepsia controlled with lansoprazole 60mg daily & endoscopically confirmed multiple duodenal ulcers. His father had a history of Zollinger-Ellison Syndrome and his sister underwent parathyroidectomy for primary hyperparathyroidism. Biochemical assessment revealed fasting gastrin level >400pmol/l (following 2 weeks of lansoprazole discontinuation), primary hyperparathyroidism (corrected calcium=3.03mmol/l with PTH=192ng/l (NR 10-65)), elevated urinary calcium excretion and normal anterior pituitary profile. Imaging assessment showed: three lesions (largest 5mm) in the head, body, uncinata process of the pancreas with normal duodenal appearance on endoscopic ultrasound; normal pancreas and duodenum on MRI and only minor enhancement in the uncinata process on triple-phase CT; two right sided parathyroid lesions on thyroid ultrasound; two abnormal signal areas in the pituitary gland on MRI. A clinical diagnosis of MEN-1 was reached, genetic screening is awaited.

Should parathyroid surgery with examination of all 4 glands and 3.5 gland-parathyroidectomy precede treatment of gastrin excess? Furthermore, the optimal management of the gastrin excess remains unclear. The options include: medical management with combination of PPI, H₂R antagonist and somatostatin analogue or exploratory pancreatic surgery with a view to long-term cure and prevention of metastasis in view of his age and likely MEN-1 diagnosis. However, for the latter radiological localisation of the pancreas to guide excision has not been successful. Should we consider venous sampling under calcium stimulation for localisation despite the small size of the lesions? Should surgery be performed and if so how should the surgeon proceed?

P030

Unresponsive hypoglycemia in a patient treated with RAD001 (Everolimus) for non-islet-cell tumor hypoglycemia caused by an adrenocortical carcinoma

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Tumoral secretion of insulin-like growth factor 2 (IGF2) may rarely cause problematic and intractable hypoglycaemia: this rare phenomenon is known as non-islet-cell tumour hypoglycemia (NICTH). It is currently envisaged that IGF2 causes hypoglycaemia by activating the insulin-receptor (IR). Recent data have indicated that inhibition of the mammalian target of rapamycin (mTOR) by everolimus (Rad001, Novartis, Basel) may disrupt the insulin-receptor signalling pathway, and there are a number of case reports of hypoglycaemia due to malignant insulinomas responding to everolimus therapy. We therefore initiated everolimus treatment, 10mg po od, in a patient who presented with severe NICTH caused by an adrenocortical carcinoma in order to attempt reduce her resistant hypoglycemia, a therapy not previously attempted. She had proven resistant to high doses of prednisolone, GH and octreotide. However, after 2 weeks everolimus had no impact on the hypoglycaemia whatsoever. The possible reasons for this may include the possibility that mTOR inhibition blocks mechanisms involved in insulin *release* rather than its *action*: everolimus has shown to decrease insulin secretion by 14%-64% and has lead to partial closure of ATP-sensitive K⁺ channels in pancreatic beta cells reducing subsequent pathway responses. Moreover, beta cell IR-mediated insulin-stimulated insulin production is disrupted by mTOR inhibition. Alternatively, IGF2 may not be acting by the classic IR: there is some evidence for IGFR1/IR hybrids, for which IGF2 has high affinity. Elevated expression of these hybrid receptors has been found in different IGF-II-phenotype tumours. Whatever the reason, our current limited data do not support a role for everolimus in the treatment of NICTH.



P031

Gastric carcinoids: prevalence in Europe and USA, and rationale for treatment with YF476, a gastrin receptor antagonist

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Background:

Gastric carcinoids (GC) are tumours arising from enterochromaffin-like (ECL) cells in the gastric mucosa. Most are caused by hypergastrinaemia, which stimulates ECL-cell growth. A gastrin receptor antagonist, YF476, prevented and caused shrinkage of GC in animal models of the condition.

Objectives: to find out if: the prevalence of GC in Europe and USA meets the criteria for an orphan disease; the drug regulatory authorities in those areas would accept YF476 as an orphan medicinal product (OMP) for GC treatment; and if the prevalence of GC is increasing.

Methods:

We searched Pubmed, the USA National Cancer Institute's SEER programme and the National Cancer Registry for England, and contacted 100 European cancer registries.

Results: The prevalence of GC per 10,000 population was median 0.32 (range 0.05–0.92) for European countries that supplied data, and 0.17 for USA, equivalent to 4,812 for the entire population. The prevalence increased 15-fold in England during 1971–2003.

Conclusions:

The prevalence of GC was well below the limit of 5 per 10,000 population in Europe and 200,000 for the whole USA population, respectively, for an orphan disease. The USA Food and Drug Administration and the European Medicines Agency have designated YF476 an OMP for treatment of GC. The increasing prevalence of GC in England matches published incidence data for the USA.

P032

Dilemmas in managing metastatic insulinoma

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A 31 year old female had a six month history of excessive hunger and lethargy after exercise. This progressed to episodes of blurred vision, confusion and altered speech. All symptoms improved with eating. She then had a tonic-clonic seizure during exercise, with a capillary blood glucose of 1.4mmol/l. After 18 hours of fasting, blood glucose was 1.9 mmol/l. Insulin and C-peptide were elevated and a sulphonylurea screen was negative. Fasting gut hormones, urinary 5-HIAA and calcium were normal. CT scan showed multiple hepatic lesions, which were positive on subsequent Octreotide scan, but no pancreatic lesions.

Arterial Stimulation with Venous Sampling confirmed insulin release following stimulation of the hepatic artery. No blush was seen in the pancreas. The peak gradient in the pancreas was 1.9 on stimulation of the splenic artery. Ga⁶⁸Octreotate PET confirmed multiple areas of intense uptake in the liver, and an area of uptake at the distal tip of the pancreas.

Octreotide was commenced, with minimal improvement in hypoglycaemia, but the addition of Diazoxide has resulted in a dramatic reduction of frequency of hypoglycaemia.

This case is unusual given the young age and short history despite the presence of metastatic insulinoma. The difficulty in detecting the primary is also worthy of comment, with even ASVS not convincingly localising, although it did confirm the functionality of the liver metastases.

Management options include hepatic embolisation, radiolabelled octreotide therapy, systemic chemotherapy or everolimus. She may need multiple treatments over time, we would welcome a discussion about the optimal sequencing of therapies.

P033

Mixed Adenoneuroendocrine Cancer (MANEC) histology and nuclear medicine imaging

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We report the case of an 81-year old man transferred to our hospital from Kuwait. He presented four months earlier to his local hospital with right hypochondrial pain, palpitations, diarrhoea up to ten times daily, nausea, anorexia and weight loss. He underwent appropriate local resuscitation and blood transfusion. A CT scan of his abdomen revealed multiple liver lesions. An US-guided fine needle aspiration (FNA) of one of these lesions reported “metastasis from neuroendocrine tumour”. Tumour markers were not elevated. An FDG-PET scan revealed hypermetabolic areas in the liver, para-oesophageal, porta hepatis and para-aortic regions. The patient was referred to our hospital for further medical management. Upon arrival, he was hypotensive, in AF and oligouric. He was actively resuscitated. He underwent a contrast staging CT scan showing a gastric neoplasm with hepatic, intra-abdominal and lymph node metastases. An OctreoScan showed avid uptake in the hepatic lesions, stomach and in a pararenal lymph node. Endoscopy revealed oesophageal candidiasis and a large ulcerating cancer in the antrum of the stomach. Multiple biopsies were obtained. Histology returned as a Mixed Adenoneuroendocrine Carcinoma (MANEC) with a small area of squamous differentiation. Chromogranin and synaptophysin positive in adenocarcinoma and endocrine areas but negative in squamous area. Mitotic index 52 per 10 HPF and Ki67 65%. Discussion: Gastrointestinal tumours displaying both exocrine and neuroendocrine differentiation are uncommon. Most of them arise in the appendix, but can also occur in colon, stomach, oesophagus, duodenum and gallbladder. Gastric MANECs are rare and this case includes MANEC with a mixed adenocarcinoma, a NEC and a squamous cell carcinoma. A component of squamous cell carcinoma has been rarely described in the literature i ii iii. The triple lineage differentiation may suggest an origin from a single pluripotential precursor in the gastric epithelium iv v vi. The case highlights the importance of biopsy over FNA. The avid uptake on OctreoScan in the high grade NEC was surprising. In an elderly patient with WHO performance score of 3 vii we recommended treatment with somatostatin analogue. If the patient had better performance status, we would otherwise recommended a platinum based chemotherapy regimen. The patient improved and was able to be discharged home.

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P034

MEN 2A with Cushing's disease

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We report a case of MEN 2A with Medullary thyroid carcinoma, pheochromocytoma, hyperparathyroidism and Cushing's disease. A 68 year old man had been diagnosed with ACTH- dependent Cushing's syndrome 10 years previously. Inferior petrosal sinus sampling (IPSS) confirmed a pituitary source and transsphenoidal adenomectomy (TSA) was performed, but no tumour was found and remained with active disease. Repeat IPSS confirmed a pituitary source of excess ACTH and following repeat surgery he was cured but rendered panhypopituitary. Subsequently he developed primary hyperparathyroidism (PHPT) and was tested for MEN 1, but no mutation was identified. However, one son was found to have PHPT in his 20s. Recently, while preparing for parathyroidectomy, an ultrasound examination of his parathyroid showed a suspicious thyroid nodule. Further investigation revealed an invasive medullary thyroid cancer with bone and liver metastases. Histology following thyroidectomy confirmed the diagnosis. In addition, bilateral adrenal nodules with elevated plasma/Urinary metanephrines were noted, suggesting pheochromocytomas. He was genetically tested for RET- oncogene which revealed a pathogenic mutation (cys⁶³⁴ Arg), confirming MEN 2A.

Cushing's syndrome due to ectopic ACTH production by MTC has been reported. Pheochromocytomas producing ectopic ACTH have also been seen in MEN 2. Rarely overlap between MEN1 and MEN2 were noted. However, to our knowledge no case has been reported in a patient with MEN2A with pituitary-dependent Cushing's syndrome, Cushing's disease. Our case suggests that in patients with Cushing's disease who have other evidence of endocrine neoplasia, if MEN1 is excluded then MEN2 should be considered.

P035

An unusual combination of imaging and histology characteristics in a patient with a lung mass and carcinoid syndrome.

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Carcinoid tumours of the lung represent up to one quarter of neuroendocrine tumours, although only 1-2% of lung cancers. Somatostatin analogues are utilised for both diagnosis and management of these tumours. We present a case in which imaging demonstrated neuroendocrine tumour deposits in the lung in a patient believed to have primary bronchogenic cancer.

A 76 year old ex-smoker presented with abdominal pain. CT imaging revealed a cavitating lung lesion, hepatic metastases and a terminal ileum abnormality. A bronchoscopy yielded no diagnostic information, but biopsy of a peritoneal mass was consistent with carcinoid. In retrospect, the patient recalled a two year history of diarrhoea and flushing; biochemical evaluation was consistent with carcinoid syndrome. An Octreotide scan highlighted foci of increased abnormal uptake in the liver and chest, despite CT imaging more suggestive of a primary lung tumour. Subsequently, biopsy of the lung mass confirmed a primary lung cancer. A lobectomy was performed – histology revealed adenocarcinoma with a background of carcinoid tumour. In fact, both could be seen on the same histological slide. Treatment with a somatostatin analogue was commenced. Eighteen months later, he remains well, with no evidence of disease progression on recent imaging.

Pentetreotide is a 111-Indium labelled somatostatin analogue, highly sensitive and specific in the diagnosis of carcinoid tumours. Here, an Octreotide scan was positive for the lung tumour, despite an initial tissue diagnosis of bronchogenic cancer. Ultimately, the excised pathology specimen demonstrated the unusual presence of both primary lung tumour and carcinoid directly adjacent to each other.



P036

A case report of a patient with metastatic cervical paraganglioma responding to the tyrosine kinase inhibitor sunitinib.

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Paragangliomas are rare [neuroendocrine neoplasms](#) that originate from neural crest cells, and are associated with increased expression of angiogenic growth factors. There have been isolated case reports describing potential efficacy with the tyrosine kinase inhibitor sunitinib. Here we report a case demonstrating an impressive clinical response to treatment with sunitinib.

A 53 yr old female initially presented with back pain and leg weakness secondary to a malignant lesion in L4. Staging investigations also revealed bilateral cervical masses and pulmonary metastases. She underwent surgical decompression and histology revealed a well differentiated neuroendocrine tumour in keeping with a diagnosis of bilateral cervical paraganglioma. She had no family history of paraganglioma and genetic analysis confirmed no evidence of mutation in *SDHB* or *SDHD*. She was unsuitable for debulking surgery, and MIBG and chemotherapy were considered to have a low probability of benefit. She was therefore commenced on sunitinib 50mg od for 4 weeks followed by 2 weeks off treatment. She tolerated treatment well other than the development of hypertension for which she was commenced on Amlodipine 5mg with good effect. On completion of the first two cycles the patient described significant symptomatic response with reduction in tumour pain, and CT confirmed evidence of shrinkage of her extensive metastatic disease. MRI spine has shown reduction in extent of her bone metastases.

This report confirms that sunitinib may be a promising therapeutic agent for the treatment of patients with advanced paragangliomas, and the results of ongoing phase II trials are awaited with interest.

P037

Monitoring patients with succinate dehydrogenase (SDH) mutations – single centre experience

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Background:

Germline mutations in SDHB, SDHC, and SDHD cause hereditary pheochromocytoma and paraganglioma, which may or may not secrete catecholamines. Whilst mutations in each subunit are associated with a particular clinical spectrum of disease, there is no clear genotype-phenotype correlation of a specific mutation, nor with penetrance of disease. Our objective was to assess characteristics of patients with SDH mutations seen in a dedicated multidisciplinary clinic at the Royal Hallamshire Hospital, Sheffield.

Methods

A retrospective observational study of patients attending from May 2005 to May 2010. All patients were assessed by one clinician (JNP). Clinical, genetic, biochemical and radiological characteristics were recorded. All patients underwent yearly biochemical screening with urinary catecholamines/metanephrines, and plasma metanephrines, and 2-3 yearly MRI of the sympathetic and parasympathetic chain using axial and coronal T1/T2 spin-echo sequences, with 18FDG-PET if needed for clinical decision making if abnormalities found.

Results

From a total of 38 patients, MRI detected all 16 tumours at baseline: SDHB 7/26, two secreting; SDHC 2/4, one secreting; SDHD 6/8 all non-secreting. Biochemistry was always normal in SDHD, abnormal in only one patient with SDHC (with tumour), but abnormal on at least one occasion, but normalised, in 7/26 SDHB without tumours. Only one patient (SDHB) presented with a new tumour at follow up. Gamma knife radiosurgery was highly effective for glomus tumours, with reduction in catecholamine secretion and resolution of symptoms.

Conclusion

MRI is effective to monitor these patients. False positive biochemistry is common in SDHB, but normal in SDHD despite the presence of tumours. Gamma knife radiosurgery can be considered for glomus tumours. No new tumours were missed by an interval of imaging every 2-3 years.

P038

Use Of The C-Peptide Suppression Test In A Challenging Case of Hypoglycaemia.

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A 39-year-old lady presented with neuroglycopenic symptoms. Hyperinsulinaemic hypoglycaemia (glucose 1.4mmol/L; insulin 3.8mU/L; c-peptide 473pmol/L; negative sulphonylurea screen) was confirmed during a fast. Endoscopic ultrasound, MRI scan and calcium-stimulated pancreatic angiography localised a functional abnormality to the uncinate process of the pancreas. Surgical enucleation was performed and histology confirmed a low grade insulinoma. A post-operative fast showed unexpected asymptomatic hypoglycaemia (1.7mmol/L), but suppressed insulin (<1.0mU/L) and c-peptide (47pmol/L) levels; and positive urine ketones suggestive of cure.

Two years later she represented with symptomatic hypoglycaemia (2.0mmol/L) and a non-elevated c-peptide levels (192pmol/L) but borderline non-suppressed insulin (3 U/L). However repeat endoscopic ultrasound, MRI scan, a ⁶⁸Gallium DOTATATE PET/CT study and calcium-stimulated pancreatic angiography were all negative.

Two further fasts were performed confirming borderline hypoglycaemia (2.4 and 2.2 mmol/L) provoked on both occasions. However, appropriate suppressions of both insulin and c-peptide levels and detectable urinary ketones did not suggest recurrent hyperinsulinaemic hypoglycaemia. A sulphonylurea screen was negative on both occasions.

In the context of ongoing symptomatic episodes, we elected to perform a c-peptide suppression test. This demonstrated a normal suppression of c-peptide. The c-peptide suppression test is a useful tool in the investigation of insulinoma. In this case, numerous apparent contradictory results have caused frustration to the clinicians, and anxiety to the patient, but evident suppressibility of β cell function during the c-peptide suppression test has provided reassurance to both.

Can we discharge her from clinic?

Should the c-peptide suppression test be a more frequently-used investigation?

P039

Are there more long term sequelae to ^{131}I -MIBG therapy with improved survival?

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Introduction:

^{131}I -MIBG is a well-established treatment modality for patients with neuroendocrine tumours (NETs), with stabilisation of disease in over 80% of patients. Documented potential sequelae of any radionuclide therapy, for both ^{131}I -MIBG and radiolabelled somatostatin analogues, include effects on bone marrow including prolonged suppression, myelodysplasia or even frank leukaemia. Incidence is thought to be low, but many reported series have limited follow-up. We present four patients treated with ^{131}I -MIBG therapy who subsequently presented with haematological disorders.

Cases:

We present four patients, 2 male and 2 female, aged 42-52 years. Their diagnoses were medullary thyroid cancer with bone metastases, von Hippel Lindau with metastatic pheochromocytoma and two patients had metastatic ileal carcinoid. They all received ^{131}I -MIBG therapy with total doses ranging from 27 to 47 GBq in 3-6 fractions. One developed myelodysplastic syndrome five years after commencing ^{131}I -MIBG therapy, one had pancytopenia nine years after his first ^{131}I -MIBG therapy. Two developed chronic myeloid leukaemia, five years and six years following initiation of ^{131}I -MIBG therapy.

Conclusion:

With effective ^{131}I -MIBG therapy, patients with NETs are surviving longer and sequelae may become apparent. A detailed review of the long-term outcomes in patients receiving radionuclide therapies would be timely, in order to evaluate long term risks and benefits. Long term ^{131}I -MIBG follow up data would be a useful comparator against other newer radionuclide therapies in use or in current trials and would provide detailed information about additional risk factors and predictors of adverse effects that may influence rational therapy choices.

P040

Factors associated with death from metastatic neuroendocrine tumours (NETs): the impact of Carcinoid Heart Disease (CHD).

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Background and aims:

Metastatic midgut neuroendocrine tumours (NETS) are rare tumours with a heterogeneous natural history. We analysed variables associated with death in these patients, with emphasis on those related to CHD.

Methods:

169 patients with metastatic midgut NETS, attending four tertiary referral NET clinics, from June 2009-June 2011 were recruited. Clinical data collected included age, gender, carcinoid syndrome and duration of diagnosis, presence and size of liver metastases; biochemical data included 24h urinary and plasma 5HIAA, plasma chromogranin A and B (CgA, CgB) and N-terminal Pro-Brain Natriuretic Peptide (NT-pro-BNP). Presence/absence of CHD (defined as a thickened, immobile and incompetent tricuspid valve) and carcinoid heart score was recorded from 2D echocardiography performed by a single operator.

Statistical analysis:

Logistic regression was used to assess the independent relationship between each variable and death.

Results:

19 patients (11.2%) screened at baseline had CHD, and 12 patients (7.1%) died during follow up. Those who died had significantly higher levels of 24h urinary HIAA:creatinine ratio ($p=0.021$), plasma 5HIAA ($p=0.001$), CgA and CgB (both $p<0.0005$). Age, presence and size of liver metastases were not found to be significant independent predictors of death.

The presence of CHD was independently associated with death: odds ratio 8.19 (95% confidence intervals 2.46-27.23). Every unit increase in CHD score, and every 100ng/ml increase in NT-pro-BNP concentration, was associated with an odds ratio of death of 1.12 (1.05-1.19) and 1.17 (1.01-1.35) respectively.

Conclusions:

Presence of CHD independently predicts death in metastatic NETs, with risk relating to CHD severity, determined by plasma NT-pro-BNP or by echocardiography (carcinoid score).

P041

Capsule Endoscopy diagnosis of multiple small bowel neuroendocrine tumours and its correlation with surgical findings.

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Small bowel neuroendocrine tumours (NETs) are often not identified on radiological imaging. Capsule Endoscopy (CE) is a new technique for examining the small bowel that can help identify and localise NETs prior to surgery. A case of a 49-year old female with metastatic liver disease from carcinoid is discussed. CT of the chest, abdomen and pelvis demonstrated only metastatic disease in the liver and no evidence of a primary tumour. Gastrointestinal endoscopy and whole body FDG PET/CT were both normal. However, wireless CE revealed multiple small bowel NETs that correlated with surgical findings of 14 separate ileal tumours. The CE and surgical findings of these primary NETs are presented; some were 'buried' under the mucosa and seen as only a white mark on the serosa, while others had overlying ulcerated mucosa. Multiple small bowel primary sites are unusual but described in the NET literature. It is often unclear whether there are multiple primary sites or small bowel metastases from a single site. This case highlights the role of CE in demonstrating the site of occult small bowel NETs. Importantly, CE can reveal the presence of multiple small bowel NETs in patients thought to only require resection of a solitary tumour. Capsule Endoscopy can improve the diagnosis and staging of small bowel NETs that directly contributes to the improved patient care.



P042

Vascular obstruction arising from mesenteric and retroperitoneal neuroendocrine cancer metastases: a case series highlighting complications and management.

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Primary neuroendocrine cancers of the gastro-intestinal tract most commonly arise within the distal small intestine or pancreas. With ileal / jejunal neuroendocrine cancers more than 50% will display metastases within the small bowel mesentery. Often such metastases will be found proximally within the mesentery - around the junction of the mesenteric root and retroperitoneum. Here they are in juxtaposition with major vascular and lymphatic structures. Less commonly locally recurrent or metastatic disease from GI neuroendocrine cancers may lie close to other major vessels. Complications arising from the effect of such metastases (or any associated desmoplastic reaction) on these vascular structures are rarely reported in the literature.

We present a series of 6 cases in which metastases from neuroendocrine cancers have caused vascular / lymphatic compression resulting in significant morbidity (3 cases of gross and rapidly accumulating ascites; 2 case lower body oedema; 1 case ascites and recurrent small bowel bleeding). The clinical features, management and outcome of these cases will be presented. In particular the potential role of vascular stenting in the management of such cases will be highlighted

P043

Comparison of the utility of biochemical markers in predicting presence and severity of Carcinoid Heart Disease (CHD).

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Background and aims:

A major complication of metastatic NETS is the development of a specific cardiac valvulopathy (CHD), conventionally screened for using echocardiography. The aim of this study was to assess the predictive value of a variety of biomarkers in screening for, and determining the severity of, CHD.

Methods:

169 patients with metastatic midgut NETS were recruited from 2008-2011. Concentrations of plasma and 24 hour urinary 5HIAA, plasma chromogranin A and B, neurokinin A and NTproBNP were analysed. All patients underwent echocardiography and presence or absence of CHD (defined as a thickened, immobile tricuspid valve) and carcinoid heart score (CHS) was recorded.

Statistical analysis:

ROC curves were constructed for each individual biomarker according to two groups (those with or without CHD) to determine their relative diagnostic accuracy. Furthermore, Spearman rank correlation coefficient was used to compare the association of plasma NT-pro-BNP, CgA, CgB, Neurokinin A, plasma and 24h urinary 5HIAA, with severity of CHD, determined by the CHS.

Results:

19 patients (11.2 %) had CHD. Significantly higher median values of NT-pro-BNP (577 vs. 88 ng/l) and chromogranin A (434 vs. 170) were found in the CHD vs non-CHD group. Neurokinin A levels were slightly higher in those with CHD (25.5, vs. 16; n=9 and n=112; p=0.07). NT-pro-BNP was best able to discriminate between the two groups with an AUC of 0.88 (95 % confidence intervals 0.80-0.95). Although the concentrations of all the biomarkers significantly correlated with the carcinoid heart score, the most significant correlation was between NT-pro-BNP and the CHS (Spearman $r = 0.42$; $p < 0.0001$).

Conclusions: NT-pro-BNP provides the best biochemical screening test to determine the existence and severity of CHD.

P044

Response of metastatic disease to adjuvant Mitotane therapy in patients with adrenocortical cancer despite suboptimal monitored levels below 14mg/dl.

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Background.

Mitotane remains the main chemotherapeutic agent for treatment of patients with adrenocortical cancer (ACC). Purportedly, plasma levels between 14-20 mg/dl are necessary in order to obtain a therapeutic response and avoid toxicity.

Methods.

Prospective database collection of clinical data for patients with ACC treated in a large University Hospital in the UK.

Results.

Between 2000 and 2010, a total of 36 patients presented with ACC (19M:17F, aged 24-78 years, mean 51.7 years) stage II (n=14) or stage III-IV (n=22), with an overall 5-year survival was <20%. Recurrence occurred in 72.2% (n=26) after a mean of 8.8 months following surgical treatment. Three quarters of patients received Mitotane chemotherapy, from between 2 and 35 months (mean 12.7 months). Mean survival in the Mitotane-treated group was 38.3 months compared to 64.0 months in those not offered adjuvant therapy. A total of 128 Mitotane assays (Lysosafe, HRA PHARMA, France) were made and 69 (54%) showed levels in excess of 14 mg/dL. Half of patients (51.9%) treated with Mitotane achieved levels >14 mg/dL at some point during their treatment. Radiological response of metastatic deposits were observed in 86% of patients (n=31) of whom only 45.1% had 'therapeutic' levels >14 mg/dl.

Conclusions.

Although monitored plasma levels of Mitotane may appear subtherapeutic, the majority of patients with ACC derive benefit from adjuvant Mitotane. However, monitoring is advised in order to avoid toxicity from levels above the therapeutic window. Intracellular factors rather than circulating concentrations of Mitotane may be more important in determining ACC responsiveness to therapy.

P045

Metastatic Paraganglioma of the Bladder

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Case History;

A 23 year old Turkish lady presented to with frank haematuria. Hypertension had been noted at the age of 17 years. She described headaches & dizziness on micturition but had not sought medical advice. There was no family history of note. Cystoscopy revealed a solid lesion in the bladder wall.

Investigations;

CT scanning confirmed the presence of an infiltrative bladder wall lesion associated with pathological enlargement of a paravesical lymph node. Histology was consistent with paraganglioma. Plasma metanephrines and urinary catecholamines were elevated and alpha-adrenergic and beta blocker treatments were commenced. ¹⁸FDG-PET and MIBG scans were consistent with paraganglioma in the bladder but also showed an area of uptake in the right femur. Technetium bone scan confirmed disease in the right proximal femoral shaft.

Results and Treatment;

The patient had a partial cystectomy with lymph node clearance and resection of the proximal femur with an oncological prosthesis fitted. Histopathology was consistent with a metastatic paraganglioma. Plasma metanephrines 4 months post surgery indicated low probability of recurrence. A gallium octreotate scan showed no evidence of recurrence. She received palliative radiotherapy to the pelvis. Results of genetic testing are awaited.

Conclusion / Discussion;

This patient had a metastatic bladder phaeochromocytoma. This is a rare but well known clinical entity with fewer than 30 cases of metastases in the literature. It accounts for only 0.06% of all bladder neoplasm's and <1% of all phaeochromocytomas. The prognosis for malignant phaeochromocytomas is significant with a 50% mortality at 5 years.

P046

Co-existing adrenocortical neoplasm and Wilms tumour presenting in a 2 year old child

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A 2 year old Arabic child presented with a left-sided leg length discrepancy and was found to have a left-sided adrenal lesion, and on further imaging was found to have renal cortical lesions existing in the same child.

A summary of the diagnoses and management are described below:

Diagnosis 1: Left sided adrenocortical neoplasm

Foreign CT on 3 July 2011 shows a 4.9 X 4.8 cm left suprarenal lesion

Pre-operative raised cortisol and androgen metabolites measured by 24 hour urinary steroid profile, raised midnight cortisol

Post-operative biochemical picture of right-sided adrenal suppression

Management:

Complete resection of left sided adrenal lesion

Weaning dexamethasone replacement therapy, reduced to 0.25mg x2/day today from 0.5mg x 2/day

For 2 monthly abdominal US surveillance and endocrine profile

Diagnosis 2: Right renal cortical solid lesions consistent with small Wilms tumour following biopsy,

Planned management:

To commence pre-operative therapy with vincristine and actinomycin D

Reassessment at 4 weeks followed by surgery at 4 weeks if lesions persist that are amenable to surgical resection. For careful discussion regarding extent of initial surgery in the context of possible cancer predisposition syndrome

Diagnosis 3: Bilateral subtle renal medullary lesions consistent with nephrocalcinosis (ultrasound assessment)

This child presents with a very unusual situation of two distinct childhood tumours, left-sided adrenocortical tumour and right-sided Wilms tumour, present synchronously in a child not previously documented to have a syndrome associated with a predisposition to childhood tumours. However, he was noted at the time of examination to have left hemi-hypertrophy, and two subcentimetre café au lait spots, and he will require further investigation by a geneticist to confirm whether Omar has a unifying diagnosis such as Beckwith Wiedemann syndrome, or another cancer predisposition syndrome. We await the opinion and results of further genetic investigation and will report on the endocrine profiles and importance of pre-operative investigations as well as the outcome regarding a genetic diagnosis in this extremely interesting case.

P047

Malignant metastatic diagnostic challenge

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Previously well 2 ½ years old girl presented with 6 weeks history of cushingoid facial features, centripetal obesity, hirsutism, and hypertension, but without virilisation. The initial investigations revealed high serum cortisol with low ACTH. Radiological investigations of abdomen and brain did not reveal presence of adrenal or pituitary tumour. MRI of the abdomen showed widespread peritoneal disease, with tumour mass surrounding liver and spleen and bulky adrenal glands. Retroperitoneum was free of tumour deposits.

Biopsy of the left upper quadrant mass was consistent with malignant epithelial tumour.

Further staging confirmed metastatic spread into the skeleton. Serum alpha feto protein was found to be extremely high.

The patient is the only child of healthy unrelated couple from Malta. There is no significant family history of cancer or endocrine disorders.

The tumour is not amenable to surgical resection and treatment with multiagent chemotherapy has been started. The hypercorticism is difficult to control despite regular metirapone and fluconazole administration. Blood pressure is controlled with antihypertensive agents.

Although the tumour has clinical and some histopathological features of adrenocortical carcinoma, the pathology is not conclusive. The elevation of serum cortisol and alpha feto protein and the uncertainty about the origin of the primary tumour make this a very challenging diagnostic and therapeutic case.