



ABSTRACT BOOK

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**UKI NETS 7TH NATIONAL CONFERENCE
30 NOVEMBER 2009**

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OC01 Heterogeneity of Proliferative Activity in Primary and Metastatic Small Bowel and Pancreatic Endocrine Carcinomas

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Introduction: Proliferative activity, expressed as the proliferation index (PI), based on Ki-67 immunostaining, is a predictor of aggressiveness of endocrine carcinomas (ECs). Tumour biopsy, in particular of liver metastases, is key to histological diagnosis and PI assessment. However, intra- and inter-tumour variability of proliferative activity could limit the diagnostic value of tumour biopsies.

Objectives: To assess heterogeneity of proliferative activity within primary pancreatic ECs (PECs) and small bowel ECs (SBECs), and liver metastases. To assess heterogeneity between synchronous liver metastases.

Material & methods: Representative sections of 8 PECs, 7 SBECs and 9 liver metastases (from 4 patients) were immunostained for Ki-67 and digitalized. Using the Aperio algorithm, the PI was assessed in 400 x 600 μ m fields (each containing approximately 2000 tumour cells), covering the entire tumour area. PI values were mapped for each tumour.

Results: The PI was assessed in a total of 1030 fields (mean per case: 54). The difference between minimum and maximum PI ranged from 2% to 30% (mean: 13.5%) and exceeded 10% in 11/19 tumours. This resulted in a shift in TNM grading in 16/19 cases (grade 1 to 2: 11; grade 2 to 3: 3; grade 1 to 3: 2). PI values within 2% of the maximum PI were present in only 1-13% (mean 4.5%) of the total tumour area, except for 3 cases, which were small and of low overall PI (\leq 3.5% in 2 cases). Current guidelines stipulate that the PI should be assessed in areas where nuclear labelling is highest, and that this is often found at the tumour periphery. In only 20% of cases, however, the PI was significantly higher in the periphery; therefore, the entire tumour area should be scanned. Findings regarding intra-tumour heterogeneity were similar in primary PECs, SBECs and liver metastases. Comparison of the maximum PI between synchronous liver metastases showed significant differences ($p < 0.05$) between 6 out of 7 tumours.

Conclusions: Marked intra- and inter-tumour heterogeneity of proliferative activity in primary and metastatic PECs and SBECs limits the use of tumour biopsies for the assessment of this prognostic factor.

OC02 Cocaine-and-Amphetamine-Regulated-Transcript (CART) Protein is a Promising Diagnostic and Surveillance Marker for Neuroendocrine Tumours

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BACKGROUND: CART was originally discovered as an mRNA transcript upregulated in the rat brain in response to psychostimulant administration. Subsequent work has demonstrated that the peptide CART is also synthesised by many neuroendocrine tumours (NETs), including islet derived transplantable tumours and human insulinomas. Preliminary work in our department suggests a role for CART as a diagnostic and surveillance marker for NETs.

AIM: To evaluate the role of CART as a diagnostic and surveillance marker for NETs.

METHODS: We measured plasma CART in 241 patients with a diagnosis of NET (103 midgut carcinoids, 80 gastro-pancreatic NETs, 29 NETs with unknown primary and 28 non-gastroenteropancreatic NETs). We also measured plasma CART in 181 controls. Plasma CART was compared in patients with clinical evidence of NETs (n=167) to those NET patients in complete clinical remission (n=34).

RESULTS: Plasma CART was significantly higher in NET groups compared to controls: [midgut carcinoids] 121 ± 15.5 pmol/L ($p < 0.0001$), [pancreatic tumours] 373 ± 42.5 pmol/L ($p < 0.0001$), [non-gastroenteropancreatic NETs] 404.2 ± 78.3 pmol/L ($p < 0.0001$) and [NETs with unknown primary] 376 ± 74.1 pmol/L ($p < 0.0001$) vs. [controls] 51 ± 1.4 pmol/L. Pancreatic NETs have higher levels of plasma CART compared to midgut carcinoids ($p < 0.0001$). Plasma CART was significantly lower in patients in clinical remission (57 ± 4 pmol/L) compared to patients with clinical evidence of disease (321 ± 27.8 pmol/L) ($p < 0.0001$).

CONCLUSION: Plasma CART levels are significantly higher in patients with NETs compared to those in controls. A diagnostic cut-off of 80pmol/L for plasma CART offers a sensitivity of 77% and a specificity of 95% for the diagnosis of NETs vs. a sensitivity of 77% and specificity of 71% for chromogranin A. Patients in clinical remission have significantly lower plasma CART than those with clinical evidence of disease. These results suggest that CART is a promising diagnostic and surveillance marker for NETs.

OC03 Genome-wide DNA methylation profiling of pancreatic neuroendocrine tumours identifies distinct methylation profiles and differentially methylated gene promoter regions associated with low, medium and high grade tumours

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Introduction

Integration of genetics and epigenetics has emerged as a powerful approach to study cellular differentiation (Mikkelsen *et al*, 2009) and tumourigenesis (Shen *et al*, 2007). The study of DNA methylation is of particular importance in cancer as causal involvement has been demonstrated and it is the most stable of all epigenetic modifications, making it a desirable marker for both early detection and treatment of tumours. Hypermethylation of CpG sites in gene promoter regions leads to decreased gene expression, if such a gene is a tumour suppressor this leads to carcinogenesis. To date, there have been no studies of genome-wide DNA methylation profiling of NETs. This study set out to determine the DNA methylation profiles of low, intermediate and high grade pancreatic NET liver metastases with the intention of identifying dysregulated biological pathways in the development of these tumours.

Methods

Ten fresh frozen sporadic pancreatic NET liver tumours (3 low grade, 3 intermediate grade and 4 high grade) were analysed using the Illumina HumMeth27 beadarray (which interrogates 27,500 genome-wide CpG sites relating to promoter regions of 14,000 genes and 100 micro-RNAs). DNA was extracted from fresh frozen tumours and 1µg of DNA bisulphite converted following standard protocols before running on the HumMeth27 array. Data analysis: Following inter and intra-array normalisation, features are identified correlating with phenotypes of interest using logistic regression analysis.

Results

Distinct DNA methylation profiles were observed in low, intermediate and high grade tumours. Initial analysis of differentially methylated regions these promoter regions has already identified genes which are differentially methylated in low and intermediate grade pancreatic NETs such as *NMUR1* (neuropeptide receptor), and the transcription factors *SOX10* and *HOXA9*. Significant difference in promoter methylation between low and high grade tumours was observed in *VEGF*, *COX5A*, *COX5B*. Differences in CpG shore methylation were observed in *MGMT* (low grade $\beta=0.86$, intermediate grade $\beta=0.53$, high grade $\beta=0.22$: $p < 1 \times 10^{-4}$ for low vs high grade). Promoter region hypomethylation was seen in all grades of tumour in *ADCY2* and *GADD45b* which correlates with reports of over-expression of these genes in mRNA expression studies of pancreatic NETs (Duerr *et al*, 2008).

Conclusions

This pilot study demonstrates that low, intermediate and high grade pancreatic NET liver metastases have distinct DNA methylation profiles. Reduced methylation of the promoter region of *MGMT* in intermediate and high grade tumours when compared to low grade infers over-expression of the gene which has implications in terms of response to chemotherapeutic agents, in particular temozolomide (Kulke MH *et al*, 2009).

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OC04 Prognostic Factors in Resected Pancreatic Neuroendocrine Tumours

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Introduction: Pancreatic neuroendocrine tumors (PNETS) constitute a heterogeneous group of neoplasms with diverse clinical and biological behaviour. Although of relatively good prognosis, many patients will succumb to the disease. Resection can provide relief of hormonal syndromes and is the only curative treatment available.

Objectives: To analyze patient and tumor characteristics of resected PNETS, and evaluate prognostic factors for survival.

Material Methods: Resected patients with pathological diagnosis of NETS of the duodenal-pancreatic region from October 1988-April 2009 were evaluated. The World Health Organisation (WHO) classification was used for tumor grading. Bivariate and multivariate analyses with logistic regression was performed with STATA 9.0 software to evaluate prognostic factors.

Results: Seventy seven patients, 21 male and 56 female, median age 55 (19-84), underwent 79 resections for pancreatic primaries. Non-pancreatic NETS were ampullary (4), duodenal (2), and paraganglioma (1). Risk factors were present in 11 (6 MEN-1, 4 Von Hippel Lindau, 1 neurofibromatosis). Forty-two (55%) patients had functional PNETS (35 insulinomas, 3 gastrinomas, 2 somatostatinomas, 1 VIPoma, 1 carcinoid); 33 (95%) had symptomatic non-functional (NF) PNETS. One hundred forty PNETS were resected, 6 patients had more than 1 tumor (median 3), median tumor size was 20 mm (5-80). Tumours were located in the head (HOP) in 44, body 16, tail 11, and were multicentric in 3. Ten had distant metastases, 9 confined to the liver. Ki-67 was <2% in 29 of 39 patients. A pancreatoduodenectomy was performed in 31, total pancreatectomy 4, distal 23 with spleen preservation in 7, central 1, enucleation 20. Additional simultaneous resections of organs with tumor invasion (5), liver metastases (9), or extra-pancreatic primaries (1) were performed in 11 (14%). Margins were positive in 10 (12.7%). Postoperative morbidity occurred in 28 (35%), 90-day mortality was 2.5% (2 patients). Seventy-five patients had well-differentiated (WD) PNETS: 22 (28%) benign, 34 (45%) uncertain behaviour and 20 (27%) carcinomas, whereas 2 were poorly differentiated. Median survival was 42 months (13-82). Of prognostic variables evaluated (age, sex, tumor functionality, risk factors, tumor size, tumor number, margin, ki-67, distant metastases, tumor grade); sex, tumor size, margin status, distant metastases and tumor grade were significant ($p < 0.05$) for survival on bivariate analysis. On multivariate analysis only tumor grade was significant. Among the WD PNETS, at 63 month median follow-up, 20 (95%) of benign tumors, 29 (85%) of tumors of uncertain behavior and 11 (38%) of carcinomas are alive.

Conclusions: PNET resections were more frequently performed in females, functional tumors slightly predominated, and PNETS were more commonly located in the HOP. Morbidity and mortality of resections were acceptable. Tumor grade was the only significant predictor of survival on multivariate analysis, correlating well in each subgroup of patients.

P001 Bland Embolisation of Neuroendocrine Carcinoma Liver Metastases: a single institution experience

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Background

A small amount of retrospective data supports the use of bland embolisation in neuroendocrine liver metastases. Despite this, it is an accepted part of the treatment for this disease. We aimed to assess the outcomes following this treatment at our institution.

Method

A list of patients who had undergone liver embolisation at the Christie NHS Foundation Trust from 1996 to 2006 was obtained from the radiology department database. A retrospective analysis of the patient case notes, electronic records, and microfilm records was performed. Outcomes assessed were symptomatic, biochemical and radiological responses, as well as survival.

Results

15 bland embolisations were performed on 11 patients with neuroendocrine carcinomas during this period. Primary sites were unknown (n=9), small bowel (n=1), and ovary (n=1). Reason for embolisation was symptomatic control (n=7) and biochemical progression (n=1). Mean duration from diagnosis to embolisation was 91.4 months. Sites of metastases were liver only (n=9), and liver and lymph node (n=2). Previous treatment included chemotherapy (n=2), surgery (n=3), interferon (n=6), and somatostatin analogues (n=11). Mean hospital stay was 9 days (range 4 to 26). Complications were pain (40%), lower respiratory tract infection (20%), carcinoid syndrome (20%) and elevated liver enzymes (20%). One patient died 12 days post procedure of a presumed pulmonary embolus. Symptomatic response was seen following 9 of 15 embolisations, median duration of response was 6 months (range 2 to 33 months). Radiological evaluation was available following 11 of 15 embolisations. Partial response was seen following 4 of 11 embolisations. Median duration of response was 8 months (range 6 to 33). Improvement in urinary 5HIAA was seen following 9 of 11 evaluable embolisations. Median survival following the embolisation was 11 months (range 0.5 to 75 months).

Conclusions

Bland embolisations were tolerated well. Symptomatic response was seen following 60% of the procedures, radiological response following 36% and biochemical response following 82%. We produced a pre and post embolisation pro-forma to be used at our institution for future bland embolisation procedures. Multi-centre collaboration will maximise collection of data on the outcomes of bland embolisation. Prospective clinical trials of this therapy should be considered.

P002 Ovarian Carcinoid

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A 64 year old nurse was noted to have a large pelvic mass and a pansystolic murmur. A pelvic ultrasound demonstrated a 25x12x18cm right adnexal mass, which was predominantly solid but also contained multiple cystic areas. A CT-CAP did not reveal any other intra-abdominal lesions. An echocardiogram showed severe tricuspid regurgitation.

This raised the possibility of carcinoid syndrome and two 24hr urine collections for 5HIAA were raised at 2128 and 2083(NR 0-100umol/24hr). A 24hr urine catecholamine collection showed only raised metanephrines (which was felt to be due to cross-reactivity of the assay with 5HIAA). She had raised ChromograninA at 930pmol/l(NR 0-60) and Ca 15-3 34 KIU/ml (0-25), but other gut hormones and tumour markers were normal.

An octreotide scan demonstrated increased tracer uptake within the pelvic mass. On further questioning, she reported a 1year history of lethargy, 1.5 stone weight loss, facial flushing and ankle swelling.

She underwent a TAH/BSO and omentectomy, under the cover of a 48hour octreotide infusion to ensure a haemodynamically stable peri-operative period.

Histology revealed a carcinoid tumour of the left ovary, not breaching the capsule (pT1a) with atypical cells arranged in trabeculae. The tumour cells strongly express CAM5.2, chromogranin, CD56, synaptophysin and NSE. Omental samples showed no evidence of metastatic disease.

Post-operatively her flushing and her ankle oedema remitted and her 24hr urinary 5HIAA was 14(0-100 umol/24hr). A repeat octreotide scan showed no residual disease and an echocardiogram showed a marked improvement in her tricuspid regurgitation.

Discussion

Ovarian carcinoid tumours are rare constituting less than 0.1% of ovarian tumours and ~1% of carcinoid tumours(1). Insular, the most common histological pattern, is associated with carcinoid syndrome and has a low malignant potential(2). As the venous drainage from the ovary connects directly into the systemic circulation, ovarian carcinoid may be associated with carcinoid syndrome even in the absence of liver metastases(3). The trabecular subtype is the rarest and is usually characterised by the absence of carcinoid syndrome(4). In cases such as this, in which the tumour is confined to the ovary, prognosis is favourable with a 5 year survival of 95% with surgery alone(1).

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P003 Still needing to combine a set of diagnostic procedures for the anatomical localization of insulinomasG. Tamagno ¹, L. McGowan ¹, S. Phelan ², K. Sheahan ², D. O'Shea ¹¹ *Department of Endocrinology & Diabetes Mellitus, and* ² *Department of Pathology & Laboratory Medicine, St Vincent's University Hospital, Dublin, Ireland*

Insulinoma represents the most common functioning endocrine tumour of the pancreas. The clinical manifestations may arise from autonomic nervous system and/or neuroglycopenic symptoms to sub-clinical presentation. The diagnosis of insulinoma is based on well defined clinical and laboratory parameters (Whipple triad and 72-hour fasting test) and can be achieved quite easily. The pre-operative tumour localization often represents the major challenge in the diagnostic management of insulinomas. Angiography with hepatic venous sampling (AHVS) after calcium stimulation (CS) was previously considered the gold standard for insulinoma localization but today is largely reserved for problematic cases. We describe two cases of insulinoma characterized by a typical clinical presentation, a positive diagnosis at fasting test, and failure in computerized tomography (CT) localization of the tumour. In the first patient, AHVS after CS correctly localized the tumour pre-operatively and the lesion was successfully enucleated. In the second patient, AHVS after CS was not successful in localizing the insulinoma, which was identified by intra-operative ultrasound and subsequently enucleated. These two cases illustrate that the diagnosis of insulinoma is based on the traditional clinical and laboratory parameters and can be readily made without other investigations. The pre-operative and/or intra-operative localization of the tumour is required for the optimal surgical approach and often represent the most relevant challenge in the management of insulinomas. AHVS after CS remains a useful procedure for insulinoma localization in selected cases. Invasive pre-operative procedures for tumour localization (AVHS after CS and endoscopic ultrasound) offer complimentary information when carried out in centres with large and longstanding experience. Both investigations should be performed in cases where tumour cannot be localized with enough certainty by a single test only. Despite their frequent efficacy, they can fail for anatomical or technical reasons and a careful intra-operative study should be performed in all patients undergoing surgery to complete the information obtained pre-operatively and to exclude the presence of other smaller lesions.

P004 Everolimus in the management of metastatic insulinoma – rapid resolution of hypoglycaemia

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A 56yrs male with coincidental immune thrombocytopenic purpura (ITP) presented in March 2003 with hypoglycaemia, high insulin and C peptide levels. CT revealed a pancreatic mass, with para-aortic lymphadenopathy and liver metastases. Treatment with diazoxide, octreotide, and 131I-MIBG (total dose 1200mCi) led to resolution of symptoms and stable disease on imaging until June 2008, thereafter his condition deteriorated. He required diazoxide 350mg/d, octreotide by continuous infusion (500mcg/d), and prednisolone 30mg/d, but additionally continuous iv dextrose, hourly glucose drinks and 2 hourly meals to maintain capillary blood glucose (CBG) over 2.2mmol/l. Temazolamide was started in January 2009, but stopped after 3 cycles owing to deterioration in the situation with persisting hypoglycaemia (9 CBG levels under 2mmol/l during 72hrs). Everolimus 10mg/d was added in February 2009. Within 48hrs of starting everolimus hypoglycaemia resolved. No CBG or laboratory glucose level was recorded under 2.2mmol/l on this regimen since then, despite discontinuation of glucose administration. Episodes of hypoglycaemia returned briefly when a transient transaminitis (ALT 165IU/l; AST 80 IU/l) led to reduction in dose of everolimus to 5mg/d but has not recurred since returning to 10mg/d. His plasma insulin was 593mIU/l before everolimus and 140mIU/l 17 days later. 3 weeks after commencing everolimus he stopped octreotide and reduced prednisolone to 10mg/d. Now 7 months after initiation of everolimus he remains free of symptomatic hypoglycaemia on everolimus 10mg/d with only additional prednisolone 10mg/d and diazoxide 350mg/d. His glucose levels range from 3.1 to 8.5mmol/l. He has lost 16kg in weight. His disease is unchanged on CT. Everolimus (an mTOR inhibitor) has been reported to achieve substantial improvement in blood glucose levels in 4 other patients with insulinomas (1). Related mTOR inhibitor Rapamycin has been reported to have similar effects (2). While mTOR inhibition downstream from the insulin receptor may reduce insulin secretion, this cannot be the explanation for all its effects in this case as circulating insulin levels remained high despite rapid achievement of normoglycaemia. It may induce insulin resistance peripherally.

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P005 Hard-to-find insulinomas: Is there a role for GLP-1 receptor scintigraphy?

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Case Report

A 55 year old primary school teacher presented with intermittent symptoms of light-headedness, confusion and recurrent collapses, that were prevented by eating. She had had a left pneumonectomy a year before for a salivary gland type lung tumour and was diagnosed with a low grade posterior fossa ependymoma.

During a 24-hour fast she became hypoglycaemic with a plasma glucose of 1.7 mmol/L, inappropriately high insulin level at 9.0 mU/L and C-peptide 834 pmol/L. Sulphonylurea screen was negative. Fasting gut peptide profile showed mild elevations of glucagon at 67 pmol/L and somatostatin of 187 pmol/L, while her corrected serum calcium was 2.16.

Dedicated CT abdominal scanning and pancreatic MRI scan did not show any lesions in the pancreas. Endoscopic US did not show any pancreatic lesions, but did reveal an enlarged lymph node. Imaging with ¹¹¹In Pentetreotide scintigraphy was negative. A ⁶⁸Ga-DOTATATE PET/CT and ¹¹¹In-DTPA Exendin-4 SPECT/CT scans were performed which showed three lesions in the tail of the pancreas.

She underwent an intra-arterial calcium stimulation test with selective angiography that revealed increased insulin secretion from the territory supplied by the splenic artery. This confirmed the presence of insulinoma in the tail of the pancreas, consistent with ⁶⁸Ga-DOTATATE PET/CT and ¹¹¹In-DTPA Exendin-4 SPECT/CT.

The patient underwent enucleation of the insulinoma. During the operation a lobulated liver lesion was identified and the liver segment 8 excised. On histology the sections from the pancreas showed a well differentiated insulinoma with Ki-67 proliferation index less than 1%. The lymph node in the tail of the pancreas on histology showed reactive features only. On histology the liver lesion proved to be a metastatic cystic adenoid carcinoma, that most likely represents metastatic spread from the lung primary lesion.

The presentation will review the indications for Exendin-4 scintigraphy for identification of hard-to-find insulinomas.

P006 A Rare Presentation of a Rare Tumour

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A 20-year-old woman was admitted to a regional hospital with back pain and hypertension (187/137mmHg). A CT scan of the abdomen and pelvis showed a large right supra-renal mass, extending into the right lobe of the liver and into the inferior vena cava. She was transferred to Addenbrooke's Hospital with a presumed diagnosis of pheochromocytoma, and phenoxybenzamine was started. Further history was obtained and she had noted weight gain and weakness over the preceding months. Examination revealed bilateral papilloedema, hirsutism and striae. Blood pressure (BP) was controlled with phenoxybenzamine and timolol. However urinary VMA was negative (x2), and as there were clinical signs of steroid excess, an ultrasound-guided biopsy of the mass was performed. Histology suggested adrenocortical carcinoma. It was decided to attempt to resect the mass and she underwent laparotomy. Histology confirmed metastatic adrenocortical carcinoma with extensive necrosis, mitoses (MIB 1 index of >30%) and lymphovascular invasion. Biochemistry demonstrated a high midnight cortisol (624 nmol/l (NR<200)), high concentrations of aldosterone (1932pmol/l (NR 100-800)) and a urinary steroid profile with a very high tetrahydro-11-deoxycortisol production (23,636ug/l). She was commenced on adjuvant mitotane with hydrocortisone replacement, and BP was controlled on candesartan. Mitotane was not well tolerated and unfortunately she was readmitted with a further hypertensive crisis. At the time CT demonstrated disease progression at the surgical margins and pulmonary metastases. Palliative chemotherapy was commenced (etoposide, doxorubicin and cisplatin), again which was not well tolerated and she was admitted with neutropaenic sepsis. She became weaker and sadly died during that admission, 2 months after her initial presentation.

Adrenocortical carcinoma is rare but has an appalling prognosis for stage 3 and 4 disease. This case illustrates some of the clinical issues with functioning tumours, causing the hypertensive crises. It highlights the need for thorough biochemical investigations of all adrenal masses. We will also highlight the importance of the multidisciplinary team in these rare complex endocrine malignancies, and the importance for the patient and her family of involvement of the Young Adult Cancer team.

P007 Phase II Study of Single Agent Capecitabine in the Treatment of Metastatic Neuroendocrine Tumours

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Background: Neuroendocrine tumours (NET) are rare tumours for which there is no standard treatment. Combination chemotherapy, often containing infusional 5-Fluorouracil (5-FU), has shown no impact on overall survival and demonstrated response rates of <30%. Capecitabine, an orally administered pro-drug of 5FU, has been shown in colorectal cancer to be better tolerated and produce an increased response compared to bolus 5FU. These are the first reported results of a multi-centre phase II study of single agent capecitabine in inoperable NETs.

Patients and Methods: Chemo-naive patients with inoperable NETs were treated with oral capecitabine 2000mg/m²/day (day 1 - 14, Q21) until disease progression or intolerable toxicity. Patients with primary pancreatic NETs were excluded from the study. The primary endpoint was biochemical and/or radiological objective response rate with toxicity a secondary endpoint. Gehans' 2-stage design for Phase II trials was adopted to minimise recruitment should the regimen demonstrate low activity.

Results: Twenty patients with NETs were recruited at three centres. Nineteen patients received at least one cycle of treatment and were therefore evaluable for response and safety. The median age was 64 years, 52% were male and the primary site of disease in 63% was the gastrointestinal tract. Octreotide therapy had been commenced prior to study entry in 42% of patients and in 5% it was started concurrently. Sixty-eight percent patients experienced stable disease (SD) on study, in 31% of these SD was maintained for > six months. Median overall survival (from start of study) was 23.7 months (95% CI 13.5 – 34.1 months) and median time to progression was 5.3 months (95% CI 2.8 – 7.8 months). There were two episodes of suspected cardiac toxicity, attributed to the study drug: one occurred following the first cycle of treatment and was fatal, the other following cycle six without sequelae. Grade 3/4 toxicities included diarrhoea (26%), fatigue (26%) and raised liver function tests (LFTs) (20%). Most patients, as expected, experienced a degree of rash/palmer plantar erythema but none were grade 3/4.

Conclusion: In this group of patients single agent capecitabine was well tolerated and should be considered as an alternative to infusional 5-FU in the management of NETs.

P008 Case Follow up: The Ups and Downs of Chromogranin A and Gastrin

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There is now a general awareness that treatment with proton pump inhibitors (ppi) may cause moderate rises in circulating concentrations of gastrin and/or chromogranin A (CgA), thus decreasing the specificity of these markers in the diagnosis of neuroendocrine tumours (NETs).

We previously reported a case of extreme rise in CgA in a 51 year old female (BD) which we concluded was due to ppi therapy alone. This conclusion with received with some skepticism. We have followed up this patient and present additional data in relation to ppi therapy. We also report a second patient, a 27 year old male (CO) who also showed extreme rise in CgA with ppi therapy. We audited all laboratory requests for CgA/gastrin in a 2 year period and monitored those that provided details of ppi treatment/withdrawal.

Patient BD had plasma CgA and gastrin concentrations of 1250 U/l and 75ng/l respectively when initially investigated (reference ranges 0-30 U/l and <100 ng/l). After ppi therapy was withdrawn CgA and gastrin fell to 22 U/l and <30ng/l. Therapy with ppi was resumed and CgA and gastrin rose to 970U/l and 175ng/l. Therapy was then changed from ppi to H2 receptor blockers and again the CgA fell to 28U/l and gastrin fell to 40ng/l.

Patient CO presented with CgA of 960 U/l and gastrin of 725ng/l while taking ppi. After ppi withdrawal CgA was 39 U/l and gastrin was 70ng/l.

On audit, only 37 request forms provided information on ppi therapy. Gastrin was measured in 36 of these samples and 18 (50%) were moderately elevated. CgA was measured in 30 samples and 22 (73%) were moderately elevated. Ten follow up samples after ppi withdrawal were received. All gastrins returned to normal. All CgA concentrations fell significantly although 4 of 10 remained above the reference range.

It is concluded that while ppi therapy may cause moderate rises in CgA, occasionally extreme rises may be observed. This should be kept in mind in the biochemical investigation of NETs. From the laboratory perspective, when information regarding acid-suppressing therapy accompanies requests for NET markers, it greatly assists interpretation of results.

P009 Surgery or no surgery in a patient with MEN 1 with an asymptomatic pancreatic mass

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This patient is a 52 year old lady with MEN 1 (mutation Exon-4 of the MEN1 gene) who presented in 2008, aged 51 years, with hypercalcaemia and a diagnosis of primary hyperparathyroidism was confirmed. She underwent a subtotal parathyroidectomy in September 2008 during which 3 parathyroid glands were removed. The histology of two of these glands revealed hyperplasia. In March 2008, abdominal CT scan revealed a 2.6 cm cystic lesion in the tail of the pancreas and two hyperechogenic lesions - one of 10mm and the other 14mm in the neck and body of the pancreas respectively. All these lesions were consistent with neuroendocrine tumours. Her fasting gut hormones are normal, apart from a raised chromogranin B at 292 pmol/L (NR <150). Octreotide scan did not show any abnormal uptake. Since this lady was so well and the lesions were not producing any active hormones, initially, it was felt that a repeat abdominal scan should be repeated at a six month interval and that surgery should be advised if the cystic lesion had increased in size or become secretory. She was on no regular medication.

The repeat CT scan of her pancreas with contrast showed no changes in appearances in any of the pancreatic lesions or in the other upper abdominal viscera compared to the previous scan and no evidence of metastatic disease or lymphadenopathy. Her fasting gut hormones remain normal apart from a persistently raised Chromogranin B and she remains well. However, even though there is no evidence of hyperfunction, once a lesion is more than 2 cm in size, the risk of malignancy/metastases increases and therefore, on size criteria, we feel that this patient should be offered surgery in the form of a distal pancreatectomy.

P010 Neuroendocrine Abstract - Is there a role for Octreotide imaging in the management of some less common pulmonary neuroendocrine tumours?

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Radionuclide imaging is an important feature in the diagnosis and management of Neuroendocrine tumours. The techniques involved demonstrate a high degree of sensitivity and specificity. Despite this, there remains a proportion of tumours which are not well visualized with this technique. This article seeks to demonstrate this by presenting two less common pulmonary neuroendocrine conditions that were not visualised on Octreotide imaging.

Case 1: Diffuse Idiopathic Neuroendocrine Cell Hyperplasia(DIPNECH)

A middle aged non-smoking female patient presented with dyspnoea and a non productive cough. Pulmonary function testing (PFT's) revealed an obstructive ventilatory pattern and a diagnosis of asthma was made. The patient improved initially on a course of anti-asthma medication and low dose steroids.

However, a subsequent CT study demonstrated multiple pulmonary nodules. The differential diagnosis for this included infection, extrinsic allergic alveolitis, sarcoidosis and other causes of obliterative bronchiolitis. The patient did not improve and as the diagnosis was still uncertain an open lung biopsy was performed. This revealed neuroendocrine cells and the features were highly suggestive of DIPNECH.

An octreotide study was performed to determine if the nodules demonstrated avidity and to look for other potential foci of disease which would be amenable to octreotide labelled radionuclide therapy, however only physiological activity was seen.

Case 2: Spindle Cell Carcinoid

The second patient was also found to have multiple pulmonary nodules following investigation of a non productive cough. At biopsy these were shown to comprise spindle cell carcinoid tissue. The patient underwent octreotide imaging 8 years following diagnosis due to progressive shortness of breath. No Octreotide uptake by the tumour was demonstrated

Discussion: Some tumours may not demonstrate Octreotide avidity and may warrant alternative imaging techniques such as MIBG for better localization.

P011 UKINETS Case submission - A case of a mediastinal paraganglioma

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A 37 year African man presented to his local hospital with a 2 month history of dry cough, shortness of breath, sweating and 10 kilogram weight loss. A mediastinal mass was found on chest radiography. CT imaging of his chest and abdomen confirmed a large central mass in the precarinal area. He had a positive mantoux reading and was treated empirically for presumed tuberculosis. There was no improvement in the size of the mass and sputum tuberculosis cultures remained negative.

Mediastinoscopy revealed a vascular lesion, which bled on biopsy. The histology revealed blood only. Similar results were obtained on CT-guided biopsy and several attempted transbronchial biopsies. On further review of his CT chest images, an unusual enhancement pattern was noted with a striated appearance in the peripheral half and a central necrotic core. The possibility of a paraganglioma was considered and he was referred for endocrine investigations. He was normotensive throughout his presentation and investigations. Hormonal investigations indicated normal 24 hour urine and plasma catecholamines. An MIBG scan demonstrated increased uptake in the mediastinal region supporting the possibility that the mass originated from neural crest tissue.

Given these results, the patient was commenced on alpha blockade with phenoxybenzamine and pre-operative percutaneous embolisation of the dominant vessels and smaller feeder vessels was performed with polyvinyl alcohol. Angiography, during this procedure, confirmed a highly vascular mediastinal mass. A median sternotomy was performed 48 hours after embolisation. A large tumour behind the ascending aorta was successfully mobilised and excised. The patient made an uneventful recovery. Histology revealed a well circumscribed tumour with no evidence of invasion. The tumour stained positively for chromogranin, NCAM and S100. This confirmed the mass as a non-secreting mediastinal paraganglioma.

Our case illustrates the importance of considering paragangliomas in the differential diagnosis of mediastinal lesions, particularly if accompanied with the characteristic radiological appearances described here. These rare tumours are hypervascular and have the potential to invade surrounding vascular structures, making surgical resection technically challenging. Pre-operative embolisation, along with adrenergic blockade, should be considered routinely in the management of mediastinal paragangliomas to improve surgical success rates and minimise complications.

P012 An unusual presentation of synchronous neuroendocrine primaries on the background of MEN1

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Background

Multiple Endocrine Neoplasia type 1 (MEN1) is an autosomal dominant disorder often characterized by endocrine tumours of parathyroid, pancreatic islets and pituitary. The presence of separate synchronous neuroendocrine tumours with different morphologies is not well described in the literature. It is well established that patients with neuroendocrine tumours have associated adenocarcinoma of separate origin and this can occur in up to 20% of patients.

Case Presentation

We report the case of a 44-year-old lady who was found to have invasive ductal breast carcinoma with multiple bony metastases. She was treated with Tamoxifen. Surveillance imaging three months later showed a lesion in the lower lobe of her left lung, and she was also noted to have a mass in her pancreatic tail. Biopsies were performed of the lung mass and pancreatic mass. This showed neuroendocrine tumours with different morphologies and immunohistochemical staining patterns. Whilst tumour cells from both foci were positive for chromogranin and synaptophysin, the pancreatic tumour cells were also positive for NSE, S100, PR and ER. The lung tumour cells, however, were negative for S100, PR and ER, but positive for TTF-1, Cam5.2, MNF, CD56 and PGP9.5. The proliferative index of the pancreatic tumour by Ki67-staining was noted to be less than 1% and mitotic activity was less than 1 per 10 high power fields. The lung tumour, however, showed Ki-67 proliferation index of 3% with no mitotic activity seen. Relevant past medical history included elevated parathyroid hormone level aged 18 years, for which she had undergone four-gland parathyroidectomy. We arranged genetic testing and she was confirmed to have MEN1.

Conclusion

The central point of interest in this case is the presence of two neuroendocrine tumors of entirely separate morphologies in a patient with MEN1. The grades of the tumors were different and this could impact on the management. In addition, she had adenocarcinoma of the breast. Due to the increased risk of co-existing tumors in these patients, any new significant mass lesions should be investigated thoroughly including biopsy, to assess the possibility of additional primary neoplasms.

P013 Classification by Grade in Gastroenteropancreatic Neuroendocrine Tumours

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Background: Gastroenteropancreatic neuroendocrine tumours (NETs) are uncommon tumours with a reported incidence of 2.5-5 per 100000 population. The recent classification system of NETs proposed by the European Neuroendocrine Tumour Society (ENETS) uses both Ki-67 labelling index and mitotic index to assign grade (low, intermediate, high). It has been adopted into routine practice but there is limited data on the relationship between these indices and their effect on classification.

Aim: To identify the relationship between Ki-67 labelling index and mitotic count

Methods: 160 NET patients, 81 midgut and 79 pancreatic had their cases reviewed. Ki-67 proliferation index, identified by staining tumour sections with MIB-1 antibody, was determined by assessing the percentage of positively staining tumour cell nuclei in 2000 tumour cells in areas with highest degree of nuclear labelling where possible. Mitotic counts (per 10 hpf) were evaluated in at least 40 fields in areas of highest mitotic activity. Grades (1 to 3) according to the new TNM classification were assigned using both indices. Correlation (Spearman r) and agreement (weighted Kappa) were calculated using Graphpad software.

Results: 63 out of 81 midgut and 61 out of 79 pancreatic NETs had complete data. A highly significant correlation was observed between Ki-67 and mitotic count in both midgut ($r=0.51$, $p<0.0001$) and pancreatic ($r=0.53$, $p<0.0001$) NETs. When assigning tumour grade, there was only agreement in 67% of midgut and 44% of pancreatic NETs. Weighted Kappas for midgut ($\kappa=0.35$) and pancreatic ($\kappa=0.34$) NETs only showed a 'fair' measure of agreement between the two indices when assigning grade.

Conclusion: This study suggests there may be a discrepancy when assigning grade of tumour in gastroenteropancreatic NETs based on Ki67 index and mitotic index. Although, as expected there is a high correlation between the 2 indices, when looking at agreement of assignment of grade, there is a discrepancy. This may have implications when proposing management strategies for patients.

P014 Clinical and biochemical features of sporadic and hereditary pheochromocytomas: an analysis of 19 cases investigated in a single endocrine centre.

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Context: Advances in the understanding of the natural history and genetics of pheochromocytomas have altered the demographics of this condition resulting in much higher rates of malignancy and association with known genetic abnormalities.

Objective: To analyse the clinical and biochemical features of sporadic and hereditary pheochromocytomas.

Design: Retrospective case-series at Guys and St Thomas's NHS Foundation Trust identified using our in house electronic database (Diabeta-3).

Main outcome measures: Clinical presentation, clinical manifestation and pathology of the tumour, catecholamine secretion, radiological features, clinical course and management.

Results: Nineteen patients were reviewed, 13 of which were sporadic (10 benign and 2 malignant) and 6 (2 benign and 4 malignant) associated with hereditary diseases (multiple endocrine neoplasia type 2 A in 2 patients from unrelated families, von Hippel-Lindau disease in 3 patients from unrelated families, and type 1 neurofibromatosis in one patient).

The mean age at diagnosis was 42.7 ± 10.7 years in the sporadic group and 30.7 ± 11.7 years in the hereditary group. There was no significant difference in the clinical presentation between the two groups. The most common presenting feature was hypertension which was found in 10 (76%) sporadic patients and 4 (66%) patients with hereditary pheochromocytomas. Bilateral tumours were found in 1 (7%) sporadic case and in 2 (33%) hereditary cases. The mean tumour size was 6 ± 3 cm in the sporadic group and 4.2 ± 0.5 cm in the hereditary group. The urine catecholamine concentration was highly variable and failed to show any significant difference between the groups.

Conclusion: These results show a high proportion of hereditary diseases among patients with pheochromocytomas. Sporadic pheochromocytomas present at a later age, are larger in size and less likely to be malignant compared to hereditary pheochromocytomas. However, according to our series, it is difficult to differentiate between the two groups based on clinical presentation, laterality of tumour, imaging and features of catecholamine secretion. Genetic and clinical testing is important and will dictate the clinical course of the disease.

P015 Management of adrenal tumours

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Aims:

To investigate the outcome of consecutive adrenal tumours and paragangliomas that were referred to a specialist adrenal clinic.

Methods:

All adrenal tumours referred to one surgeons practice 2000 and 2008 were retrospectively analysed. Clinic notes, bloods, radiology and histology were collated to determine the presentation, investigations, diagnosis and management.

Results:

101 patients were identified with adrenal tumours or extra-adrenal paragangliomas. 58(mean age 67yrs; range 37-87yrs) were managed non-operatively while 43 (mean age 53yrs; range 26-80yrs) were managed operatively. In comparison, 27/43(63%) of surgical patients had evidence of increased adrenal hormone secretion and only 14/58(24%) of those not operated on. All patients were investigated for secretion.

All patients had at least one CT scan for which non-operative tumours (mean 2.8cm; range 0.5-7cm) were found to be on average smaller than operative tumours (mean 4.5cm; range 0.9-12.2cm).

Type	Surgical intervention Number (mean size cm, mean age in years)	Non-surgical intervention Number(mean size cm, mean age in years)
Benign adenomas	2 (6, 53)	36(2.4,69)
Conns	5(1.67, 51)	4(2.1,53)
Cushings	14(4.2, 55)	6(2.6, 72)
Pheochromocytomas /paragangliomas	17(5.4,54)	0
Metastatic cancer	0	6(3,65)
Adrenocortical carcinoma	2(8, 38)	2(inoperable)

Conclusions:

Difficult clinical decisions are a reality for patients with adrenal lesions with subclinical cortisol secreting tumours, conn's patients with equivocal investigations, some large very slow- growing non-secreting tumours and the elderly with multiple co-morbidities. These should be managed in a speciality clinical with a multi-disciplinary team approach and a protocol driven investigative practice.

P016 Bilateral Pheochromocytomas and Pancreatic NET– what is the syndrome?

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A 6 year old boy presented to the paediatric endocrinology team with a history of hypertension. Investigations demonstrated bilateral adrenal pheochromocytomas for which he underwent bilateral cortical-sparing adrenalectomy. He was raised by his grandmother hence his immediate family history was unknown but there were no clinical or biochemical features to suggest a diagnosis of MEN2, VHL or NF1. Subsequent analysis of the *RET*, *VHL*, *SDHB* and *SDHD* genes was normal. A routine annual catecholamine screen aged 17 showed a mild increase in normetanephrine, hence he underwent abdominal MRI and MIBG scans. The MIBG scan showed physiological tracer distribution only and the MRI did not confirm any abnormalities in the region of the adrenal glands. However, note was made of a 3cm mass in the head of the pancreas, compatible with a neuroendocrine tumour. Chromogranin A [74 pmol/L (normal<60)] and pancreatic polypeptide [374 pmol/l (normal <300)] levels were mildly raised but the rest of the fasting gut hormone profile was normal. Histological review of a liver biopsy specimen taken at subsequent laparotomy showed clusters of cells containing abundant foamy cytoplasm with small, pleomorphic nuclei; on immunohistochemistry these were positive for chromogranin, neuron-specific enolase and synaptophysin as well as AE1/3 and inhibin. The appearances were consistent with metastatic well-differentiated neuroendocrine carcinoma. The combination of bilateral adrenal pheochromocytomas and pancreatic NET is typically seen in the context of Von Hippel Lindau syndrome but rare inherited cases of this combination are described in the absence of VHL. We presume a familial basis for his disease in view of the multi-organ involvement and young age at presentation; however, the mutational basis of this condition is not known and we welcome suggestions of potential genetic targets.

P017 Night blindness in carcinoid: an uncommon complication

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Vitamin deficiencies may develop in patients with carcinoid for a variety of reasons. Best described is niacin deficiency due to diversion of tryptophan synthesis to serotonin, while other vitamin deficiencies may be caused by malabsorption.

Case report

A female patient presented in 2002 at the age of 52 with diarrhoea and abdominal pain. Investigations revealed a right iliac fossa mass due to a carcinoid tumour with mesenteric and pelvic lymph node metastases and peritoneal seedlings. She underwent right hemicolectomy, cholecystectomy, omentectomy and lymphadenectomy. In 2004 she developed bowel obstruction and had small bowel resection sigmoid colectomy and ileostomy. Since her diagnosis she had been established on somatostatin analogue therapy and on follow-up has stable disease. Over the following 3 years she lost weight. In 2007 review of her nutrition revealed a normal albumin, low vitamin D, normal calcium, marginally raised PTH, normal vitamin E, normal selenium and manganese. Her stoma output was approximately 1.5L per day. She commenced supplements (Ensure, Forceval and Ketovite). In May 2008 she complained that her vision was poor at night and was aware of a ring scotoma in dim illumination. On ophthalmological assessment she had normal visual acuity and colour vision, but electrophysiology showed abnormal dark adaptation and reduced rod function. She received intravenous vitamin A infusion followed by oral vitamin A supplements. Her symptoms resolved within a few weeks.

Vitamin A deficiency developed most likely due to short bowel syndrome. This complication occurs rarely in patients with neuroendocrine tumours. Early diagnosis and treatment reverses the visual defect.

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A case of vitamin A deficiency secondary to pancreatic carcinoid tumour which resulted in night blindness is presented.

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Reversible night blindness in a patient with neuroendocrine tumour of pancreas.Appaswamy S, De Silva D, Tyagi A, Grocott LE, Heath PD, Gillow T.

P018 Diagnosis and Localisation of Insulinoma: The value of Modern MRI in Conjunction with Calcium Stimulation Catheterisation

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Objective

To review the diagnostic features of insulinomas and the localisation accuracy of differing diagnostic modalities at a single tertiary referral centre.

Design

Cross-sectional, retrospective analysis of patients with insulinoma 1990-2009, including sporadic tumours and those in patients with multiple endocrine neoplasia (MEN) syndromes.

Methods

Patients were identified from a database, and their case notes and investigation results reviewed. The accuracy of tumour localisation by computed tomography (CT), magnetic resonance imaging (MRI), octreotide scanning, endoscopic ultrasound and calcium stimulation was compared to histologically-confirmed location following surgical excision.

Results

Diagnostic data were reviewed on 33 prolonged supervised fasts (up to 72 hours), the majority being terminated within 48 hours.

Forty-six instances of biochemical and/or histologically proven insulinoma were identified in 41 patients. Of the 31 sporadic cases, 6 were managed medically. Of the remaining 25 (for whom surgical localisation was available), 19 had CT scanning (76%) and 23 had MRI scanning (92%). There was successful localisation in 12 (63%) by CT and 19 (83%) by MRI scanning respectively. When considered together, such cross-sectional imaging correctly localised 92% of lesions with no false positives.

For the subgroup of patients with sporadic tumours managed non-operatively, 5 had an uncertain tumour site or patient preference for conservative treatment. Inclusion of these in the localisation analysis results in an amended localisation rate on cross-sectional imaging of 23 out of 30 patients (77%).

Radiolabelled octreotide scanning was used in 17 cases correctly localising 8 (47%) cases, with 2 false positives (12%). Eighteen patients underwent endoscopic ultrasound; 10 lesions (55%) were correctly identified with 2 false positives (11%). Twenty-two patients had calcium stimulation testing of which 6 (27%) did not localise, 15 (65%) correctly localised and 1 (5%) incorrectly localised.

Conclusions

Preoperative localisation of insulinomas remains challenging in spite of recent advances in localisation techniques. Radionuclide imaging and endoscopic imaging techniques were not very useful in our series, but may be useful in selected cases. A pragmatic combination of CT and especially MRI has been shown here to predict tumour localisation with high accuracy, and with recent technical advances would seem to offer much better localisation than has previously been reported. Calcium stimulation currently remains valuable in providing an additional functional perspective.

P019 RAD001 for small bowel carcinoid

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Experience at one year of the only UK case of small-bowel carcinoid syndrome treated with continuous RAD001

A 62 year old man was referred from Wales for management of carcinoid syndrome. He was diagnosed with carcinoid syndrome in October 2006 based on CT abdomen and elevated urinary HIAA. The CT abdomen showed small bowel carcinoid with desmoplastic infiltration of mesentery at two sites. He had occasional diarrhoea but did not have any flushing or weight loss when he presented to the neuroendocrine clinic. Magnetic resonance imaging showed multiple lesions suggestive of carcinoid disease. He had resection of the small bowel primary on October 2007.

5HIAA levels were persistently high (250) following surgery and chromogranin A was greater than 1000. Magnetic resonance imaging was repeated and it showed 20% increase in the size of the lesions (maximum size 4cm with total of 15 lesions). Octreoscan was strongly positive. The patient was worked up for a study using RAD001 and Sandostatin LAR but after cancellation of the study he was started on named-patient RAD001 in a dose of 10mg per day orally in July 2008.

Side effects were mouth ulcers and an episode of pneumonitis, after four months of treatment. The pneumonitis was treated with antibiotics and reduction of dosing of RAD to 5 mg daily, with radiological and clinical improvement. Urinary HIAA increased while on treatment to 1000 at 9 months then decreased to 729 at 11 months. Chromogranin A level decreased from 1000 to 623 at 11 months. RAD001 was then increased to 7.5mg od, without further side effects

At 11 months he was asymptomatic with very slight flushing but no diarrhoea or weight loss. He was initially tried on octreotide sc but did not tolerate this well because of abdominal pain. He was subsequently started on lanreotide 30mg monthly. The dose of RAD001 has been increased again to 10 mg per day. The size of liver lesions has remained unchanged over the period of therapy. This case demonstrates that with dose adjustments it is possible to reduce side effects from RAD001 and that disease stabilisation can occur. This is the only patient in UK who has been treated with this drug for carcinoid syndrome for more than one year.

P020 A comparison of 3 cases of paediatric adrenocortical carcinomas within a single centre: prognosis , management and controversies

Authors

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Abstract

Paediatric adrenocortical tumours (ACT) are especially rare in childhood with tumour size (>100g)- rather than histopathology – recognised as (poor) prognostic indicator. They are often associated with p53 mutations and tumour predisposition syndromes (e.g. Li-Fraumeni). Up to 80% present with adrenal androgen excess.

We compare treatment outcomes of 3 children with large (>200g) aggressive, hypersecreting, right adrenocortical cancers (ACC) invading the IVC +/- right atrium and presenting to one centre with virilisation, a palpable abdominal mass, hypertension (refractory in case 1) and Cushing's syndrome, 12, 4 and 0.1 years ago.

2 males and 1 female all had proven p53 gene mutation positivity and were staged as aggressive 11B disease based on tumour size and mitotic index post-operatively. All however achieved biochemical remission within 3-4 postoperative weeks but their management and outcomes differed.

Case 1 (male) aged 3.4 years (1997) underwent complete microscopic surgical resection and had 1 cycle each of OPEC and JOE chemotherapy. He later developed a second sarcoma and currently has a third cerebral glioblastoma multiforme tumour.

Case 2 (male) aged 7.5 years (2005) underwent macroscopic surgical resection without nephrectomy (with tumour spill) and 4 cycles of adjuvant cisplatin and etoposide chemotherapy as well as mitotane. He relapsed on therapy and died within one year of diagnosis.

Case 3 (female) aged 0.9 years (2009) underwent right adreno-nephrectomy under bypass with macroscopic clearance confirmed on MR but residual microscopic disease at tumour margins. Adjuvant cisplatin, etoposide and mitotane with lymph node clearance was recommended but declined by the family, pending biochemical relapse

Comment: Consensus best practice guidance on staging and management of paediatric ACT has recently (2005) recommended platinum based chemotherapy together with mitotane for poor prognosis disease (≥11B). However effectiveness has not been demonstrated; mitotane is poorly tolerated with potentially irreversible adrenotoxicity and masks tumour markers of recurrence, whilst chemotherapy carries its own risk-benefit profile. Extent of surgical resection is the most likely important prognosticator.

The ethical difficulties in advising therapies for rare childhood tumours with limited chemosensitivity and tumour predisposition are manifold, differ from adult practice and mandate international registration collaboration for future level 1 research.

P021 A case of pheochromocytoma with negative MIBG scintigraphy

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We present a case of a 20 year old Psychology student who presented with a two year history of sweating. His blood pressure had been high at 150/100 at his surgery. He had recently reported abdominal pain, which prompted his general practitioner to request an ultrasound scan of his abdomen. The ultrasound revealed a right sided suprarenal mass of 4.9x3.4x4.2cm. He was subsequently referred to endocrinology for further management. A CT scan of his abdomen confirmed a 4.6 cm right sided adrenal lesion. Two sets of 24 hours urinary catecholamines showed markedly elevated levels of noradrenaline of 24.47 and 24.82 umol (NR 0.00-0.50) and a mildly elevated dopamine of 3.87 and 3.69 umol (NR 0.00-2.70). Plasma noradrenaline was found to be markedly elevated at 80.9 nmol/l (NR 0.00-0.50). MIBG scintigraphy was performed; however there was no increased MIBG uptake in the lesion. A gallium-68 dotatate scan was subsequently performed which confirmed a moderate sized adrenal lesion with a necrotic centre. He was commenced initially on phenoxybenzamine alone, with subsequent addition of atenolol. The patient underwent a laparoscopic adrenalectomy, the histology of which is awaited.

This case highlights the limitations of MIBG scintigraphy. Due to similarities between MIBG and noradrenaline, it has been commonly used in the diagnostic pathway of pheochromocytoma for over 20 years. However, MIBG scintigraphy has been shown to have reduced sensitivity in some familial paraganglioma syndromes, malignant disease and extra-adrenal paragangliomas (Havekes et al, 2008). (123)I-MIBG has a reported specificity of 99% and sensitivity of 90% (Brink et al, 2005). Other data suggest that 123I-MIBG scintigraphy is negative in 15% of cases of benign pheochromocytoma and 50% of cases of malignant pheochromocytoma (Mackenzie et al, 2007). Until recently, (18)F-fluoro-deoxy-D-glucose ((18)F-FDG) has been commonly used in the assessment of neuroendocrine tumours. Gallium-68 is a promising new PET tracer which may be superior to 18-F-FDG, due to its short half-life and flexible labelling ability to a wide range of peptides and antibodies (Khan et al, 2008).

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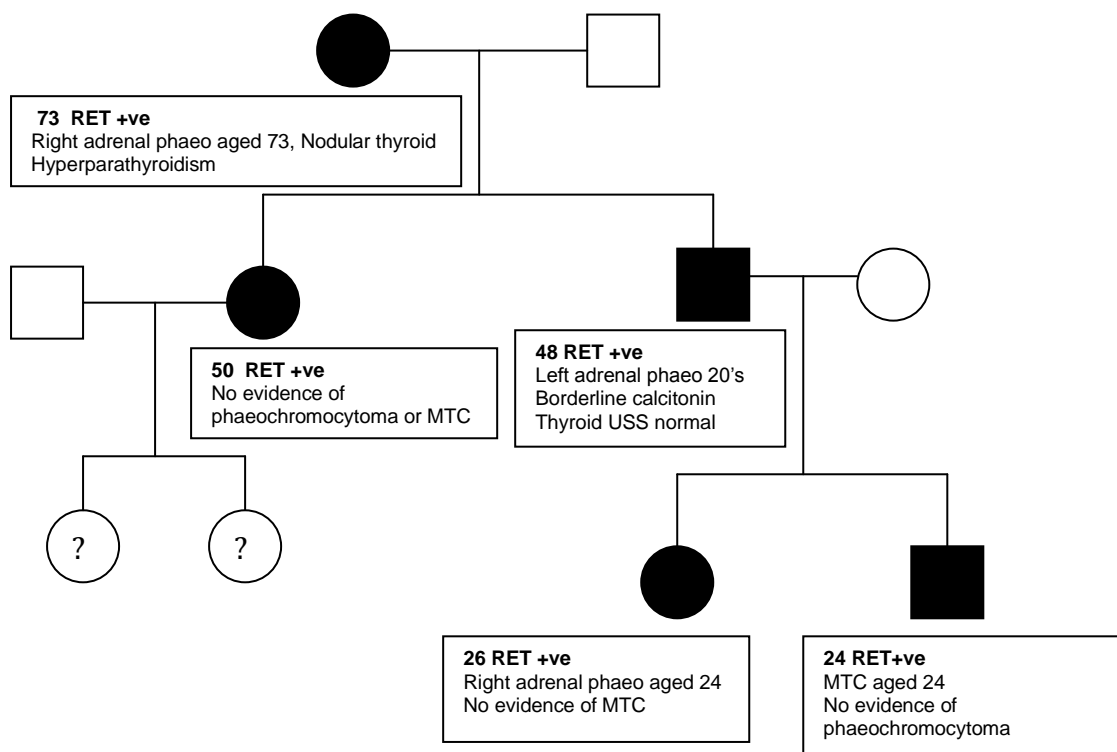
P022 Youngest and oldest phaeochromocytoma and variable penetrance of medullary thyroid cancer (MTC) across three generations in a kindred presenting with MEN2a - challenges to current guidelines.

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Introduction: In MEN2a there is usually a tight correlation between genotype and penetrance of phaeochromocytoma, MTC and hyperparathyroidism. This has particular relevance for the timing of prophylactic thyroidectomy. We present five family members with MEN2a who have expressed very different clinical phenotypes.

Kindred: The proband presented in 2008 aged 25 with a right-sided adrenal phaeochromocytoma. Genetic analysis was in progress because of her young age and because her father had a phaeochromocytoma excised twenty years previously, when her 73 year-old Grandmother presented to a district hospital with collapse. The proband remarked to her grandmother that she had identical symptoms to her own presenting features, and investigation revealed a right adrenal phaeochromocytoma. By 2009 genetic analyses revealed c.1826G>A, p.Cys609Tyr mutation in exon 10 of RET proto-oncogene in five family members (Fig). At the time of initial investigation no family members had clinical expression of MTC: The grandmother has normal serum calcitonins and a 5mm benign thyroid nodule. The brother had an abnormal pentagastrin stimulation test and has MTC on thyroid FNA.



Discussion: Current guidelines recommend thyroidectomy before 5 years of age in patients with 609Y mutation. Only one individual of this kindred has clear evidence of MTC. Despite reports showing a lower incidence of phaeochromocytoma in individuals with codon 609 mutations, three members of this family have had phaeochromocytoma. To the best of our knowledge, the grandmother and proband are the oldest and youngest presentations with phaeochromocytoma with this mutation. Remarkably, the grandmother has no evidence of MTC. This family challenges the practice of risk stratification according to specific mutation, raises issues over the appropriate management now of their thyroids, and highlights the need for clinical vigilance and further research into factors that may modify penetrance of a mutation in MEN2.

P023 A Very Malignant Pheochromocytoma - management challenges

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A 46-year-old Caucasian man presented with a 4-week history of abdominal discomfort. He had no other significant symptoms. He had a history of hypertension for 10 years that was well controlled on doxazosin, atenolol and nifedipine. His alcohol consumption was 70 U/wk. There was no family history of note to suggest a genetic abnormality.

Examination showed him to be thin, anxious and tremulous with a pulse 76/min and BP 116/84mmHg. CT scan revealed a 14 cm heterogeneous left adrenal mass with invasion of the left renal vein. Hypervascular lesions were noted in the liver raising the possibility of metastases. MIBG scan showed patchy high uptake in the adrenal lesion but not in the liver. Twenty four hour urine meta-adrenaline and nor-adrenaline levels were raised at 12.7 micromol/mmol(creat)(Reference range<0.70) and 3055 mmol/S (0-500nmol/S) respectively. His doxazosin was changed to phenoxybenzamine.

A repeat CT scan just prior to surgery (8 weeks after first CT scan) showed a new 2.5 cm possible metastatic lesion in the right lobe of the liver. He had an acute pulmonary embolism while awaiting surgery, which was treated with low molecular weight heparin. He underwent surgery that involved removal of the large adrenal tumour (1.7kg), splenectomy, left nephrectomy and removal of thrombus from the inferior vena cava. Histology was consistent with malignant pheochromocytoma. He recovered well from the surgery. MIBG scan done 4 weeks after surgery did not show pathological uptake in the liver. This excluded therapeutic use of MIBG. A PET scan showed a 3.4 cm liver lesion with multiple smaller deposits in the liver, lungs and supra and infra diaphragmatic lymph nodes. He was referred for chemotherapy, however whilst awaiting this, his condition deteriorated rapidly with worsening liver function and ascites. He died within 3 days of this admission (6 months from diagnosis).

Management of a rapidly progressive malignant pheochromocytoma is complex as the response to treatment(s) can be variable and unpredictable. There are limited chemotherapy options post surgery including MIBG with variable success rates documented in the literature. This case highlights the aggressive and rapidly progressive course of malignant pheochromocytoma and difficulties in its management.

P024 Hepatic Arterial Embolism: A Novel Approach to Carcinoid Syndrome

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The prognosis in patients with carcinoid heart disease and advanced hepatic metastases is generally poor. The mean five year survival is less than 30%. Over the last decade new diagnostic and treatment modalities have resulted in improved quality of life and probable increase survival time.

Case:

We present the case of a 75yr old Caucasian lady who was initially diagnosed with carcinoid syndrome age 66 in 2000 following a 10 month history of chronic diarrhoea, profound flushing and weight loss. CT abdomen revealed a primary lesion in the right iliac fossa with multiple liver metastases. 24hr urinary 5 hydroxyindoleacetic acid (5-HIAA) was elevated at 766 (NR 0-40). Octreotide labeled scintigraphy demonstrated intense uptake in the liver, but there was no uptake in the primary lesion. She was commenced on a somatostatin analog which initially controlled symptoms, with a reduction in 24hr urine 5HIAA to 78 at 4 months. Radiologically there was no reduction in tumour size. Subsequently her symptoms steadily worsened, despite titrating dose of octreotide, with the addition of increasing shortness of breath. An echocardiogram in 2003 showed severe tricuspid regurgitation, with mild pulmonary and aortic regurgitation and impaired left ventricular function.

In 2005, 24hr urine 5HIAA had increased to 732. CT abdomen showed further progression of the hepatic metastases. Following discussion at a multidisciplinary meeting the patient proceeded to have hepatic arterial embolisation. This successfully reduced tumour burden and symptoms, with repeat 24 hr urine 5HIAA of 297. Unfortunately 18 months later her symptoms progressed, she also had a new metastatic mediastinal lesion. In 2008 she underwent further hepatic embolisation. Currently her symptoms are under control on lanreotide 120 mg 3 times a-week and creon. Last imaging reveals stable liver metastases.

Conclusion:

This patient has survived 10 years with known carcinoid syndrome, 6 years with known carcinoid heart disease; she is independent and has a reasonable quality of life. The fact that she has outlived the typical life expectancy adds to the evidence that novel treatment strategies such as hepatic arterial embolisation improve mortality data in patients with advanced carcinoid.

P025 Transient multifocal hepatic steatosis mimicking recurrence of insulinoma: case report

Ben Whitelaw, Matthew Allum, Sarah Brewster, Dylan Lewis, Pauline Kane, Simon Aylwin, Alan McGregor

Case Report

A previously well 44 year old lady presented with episodes of hypoglycaemia. Controlled fasting demonstrated hyperinsulinaemic hypoglycaemia. Subsequent imaging revealed a 4cm mass in the tail of the pancreas with no evidence of metastasis. Partial pancreatectomy was performed and histology confirmed an insulin positive neuroendocrine carcinoma, with some local lymphovascular invasion. The patient made a good recovery, though post-operatively developed impaired glucose tolerance. She remained well for the next two years and initial interval CT scanning showed no evidence of recurrence.

Three years after surgery a routine CT scan demonstrated multiple new liver lesions, thought likely to represent metastases. Clinical assessment suggested no further hypoglycaemic episodes, but conversely, she was found to have diabetes mellitus.

Diabetes treatment was commenced and a liver biopsy was planned. Repeat CT scan after ten weeks demonstrated resolution of many of the liver lesions. Biopsy was not performed. Subsequent MRI scan revealed only a few tiny lesions, not visible on the in-phase scan. These were felt to represent focal steatohepatosis. There were no features of tumour recurrence. The patient remains well and under follow up. Her diabetes, thought to be due to pancreatic endocrine insufficiency, is managed with twice daily insulin.

Discussion

Pancreatic insulinomas are rare neuroendocrine tumours. The overall risk of recurrence after surgical resection is 5-8% over 10 years. Risk factors for recurrence include lymph node metastases, lymphovascular invasion and the presence of MEN-1 syndrome.

Our case report describes apparent radiological recurrence of the neuroendocrine tumour with multiple hepatic lesions. The radiological findings were subsequently found to be due to multifocal hepatic steatosis, a rare finding known to mimic metastatic disease.

The causes of multifocal hepatic steatosis are not fully understood. Focal hyperinsulinism in the liver is the best described mechanism, and there are case reports of focal hepatic steatosis surrounding metastatic insulinoma tumours. Multifocal hepatic steatosis has also been described in the presence of poorly controlled diabetes and we suggest it is the dominant mechanism in this case.

P026 UKINETS 2009 Abstract Submission - Adrenocortical Carcinoma (ACC): The Range of Appearances on CT & MRI

Authors:

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Background:

Adrenocortical carcinoma (ACC) is a rare, aggressive tumour arising from the adrenal cortex. Recognition of the typical clinical and imaging findings is imperative for early diagnosis, prompt intervention and improved survival. Imaging is integral in determining the extent of local and distant tumour spread to guide surgery and further patient management.

Content Organization:

This educational review will briefly discuss the epidemiology; clinical, biochemical and pathological features of ACC. We will illustrate typical and atypical appearances on CT & MRI with a discussion of the differential diagnosis and description of specific discriminating features. We will also outline the specific information required by the endocrinologist, oncologist and surgeon for further treatment planning.

Summary:

The imaging appearance of ACC is diverse due to the variable presence of necrosis, haemorrhage, calcification and intracellular lipid content. Other pathologies (eg. malignant pheochromocytoma, metastases, composite tumours, ganglioneuromas, infection or congenital adrenal hyperplasia) can simulate ACC. Familiarity with typical and atypical imaging appearances, taken in conjunction with clinical information, helps to suggest accurate diagnosis and appropriate management.

P027 Using echocardiography to investigate prevalence of carcinoid heart disease and provide evidence of abnormal myocardial motion in patients with carcinoid disease

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Introduction

Carcinoid heart disease occurs in 15-70% of patients with metastatic midgut carcinoid disease. This is typified by the development of right sided valvular and endocardial fibrosis due to the action of serotonin (5-hydroxytryptamine). The left sided valves are only affected in 10% of cases. Tissue Doppler imaging (TDI) is an echocardiographic technique allowing assessment of myocardial motion. TDI has been used to identify early changes in myocardial motion in many different cardiomyopathies.

Aims

1. Identify the prevalence of carcinoid heart disease in our cohort of patients with metastatic midgut carcinoid disease and/or carcinoid syndrome
2. Identify abnormalities in myocardial motion in patients with carcinoid disease compared with normal controls.

Methods

50 patients with metastatic carcinoid disease and/or carcinoid syndrome and 10 normal controls had detailed echocardiographic studies performed by a single operator. Continuous variables were compared using a student t-test.

Results and discussion

4 patients (8%) had shortened, immobile and thickened valves on 2 dimensional echocardiogram typical for carcinoid heart disease. This low figure may demonstrate earlier diagnosis and/or better management of carcinoid disease, particularly strategies reducing circulating levels of serotonin.

TDI analysis in these 4 patients showed increased right ventricular (RV) wall motion (RV peak systolic strain -33.4%vs-25.9%, $p<0.007$) and decrease in left ventricular (LV) wall motion (LV peak systolic strain rate -1.29l/s vs-1.45l/s, $p<0.03$) when compared with carcinoid patients without carcinoid heart disease. An increase in RV motion would be expected as a compensatory response to the valve dysfunction. The reduction in LV motion may represent fibrosis.

Comparing LV motion between the carcinoid group and controls revealed significant reductions in systolic motion (peak systolic velocity 6.01cm/s vs 6.81cm/s, $p<0.01$) and diastolic motion (peak early diastolic velocity -6.38cm/s vs -8.4cm/s, $p<0.004$). This suggests a negative effect on LV myocardial motion in patients with carcinoid disease which may be evidence of fibrosis.

Conclusions

The prevalence of carcinoid heart disease as defined by the 2 dimensional echocardiogram is low. TDI demonstrates abnormalities LV myocardial motion in patients with carcinoid disease compared with controls.

P028 Localisation of metastatic parathyroid carcinoma by ¹⁸F FDG PET scanning

C.J. Gardner, H. Weissman, C Warburton, H. Carr, I.A. Macfarlane, D.J. Cuthbertson

We describe the case of a 47 year old man who was diagnosed with parathyroid carcinoma in 1989. He underwent radical neck dissection and required 2 further procedures for local recurrence. In 2001 a renal transplant was carried out for renal failure secondary to nephrocalcinosis. Serum adjusted calcium remained stable during follow up until 2008, when his biochemistry demonstrated primary hyperparathyroidism (adjusted calcium 2.82mmol/l, parathyroid hormone 29.9pmol/l). The patient was otherwise fit and well, and clinical examination was unremarkable. Further investigations including neck ultrasound, Technetium 99m-sestamibi scanning of the neck and mediastinum, and upper body Octreotide SPECT/CT were unremarkable. His serum calcium continued to increase despite treatment with a calcimimetic, cinacalcet. CT of the chest demonstrated a 1x1.5cm nodule in the apical segment of the lower lobe of the right lung, not amenable to percutaneous biopsy. ¹⁸F-FDG PET scanning demonstrated increased FDG activity in the nodule with SUV maximum of 3.2. The nodule was removed by open thoracotomy with immediate and sustained normalisation of the serum calcium (post operative PTH 6.1pmol/l, adjusted calcium 2.04mmol/l). Histology demonstrated metastatic parathyroid carcinoma. The patient has subsequently been screened for HRPT2 mutations linked to sporadic parathyroid carcinoma.

Parathyroid carcinoma is an uncommon cause of hyperparathyroidism, forming 1-5% of all cases of primary hyperparathyroidism. Metastases may occur many years after original diagnosis, and occur most commonly in lung (40%), cervical lymph nodes (30%) and liver (10%).

Technetium 99m-sestamibi has been shown to be effective in locating metastases preoperatively with a sensitivity of 79%, however no single imaging modality successfully locates all foci. PET can be useful in locating foci of parathyroid adenomatous tissue in the neck and mediastinum in patients where conventional imaging has failed.

We conclude that all cases of parathyroid carcinoma need lifelong surveillance. Distant metastases are common, and should be sought if local imaging is normal in the face of abnormal biochemistry. Functional imaging with ¹⁸F-FDG PET/CT has a complementary role in the management of such cases where conventional imaging has failed to localise the tumour.

P029 When and how to treat that is the question – a case of metastatic glucagonoma

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A 51 year old man presented in 2004 with Necrolytic migratory erythema and diabetes. Fasting glucagon was elevated and CT scan revealed a mass in the tail of the pancreas, which was also found to be octreotide avid. There was additional octreotide uptake in the right lobe of the liver but CT and MRI did not confirm any hepatic pathology. He underwent a laparoscopic resection with normalisation of his glucagon levels and resolution of his rash.

However in 2006 surveillance CT revealed a recurrent mass in the tail of the pancreas, adjacent to the site of previous surgery, again with no evidence of liver metastases. Fasting gut hormones were normal. An open distal pancreatectomy and splenectomy was performed and histology confirmed recurrent neuroendocrine tumour with low Ki67 positivity but >90% staining for p53.

In 2007 CT scan showed 3mm nodules in the liver and an MRI 6 months later showed multiple liver metastases the largest of which was 2cm. Fasting gut hormones remained normal.

By 2009 the liver lesions had progressed, the largest now measuring over 8cm, and are octreotide avid, with no evidence of extra-hepatic disease. Chromogranin A & B are both elevated, but with only minimal elevation of his glucagon. However he remains asymptomatic, with no recurrence of his rash. The patient has always been keen to follow a more conservative approach to management.

Questions for the panel are:

1. Should he receive anticoagulation?
2. What therapeutic intervention, if any, should he receive, given the rapid progression of his liver metastases, but lack of symptoms?

P030 Selective internal radiation treatment (SIRT): a new modality for treating patients with neuroendocrine tumour (NET) hepatic metastases

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Background:

Limited effective treatment options are available for patients with inoperable neuroendocrine tumour (NET) liver metastases. Selective Internal Radiation Treatment (SIRT) is emerging as a new treatment modality in the management of patients with un-resectable liver metastases. The unique pattern of hepatic arterial flow providing the overwhelming majority of the tumor blood supply is the fundamental concept behind the intra-arterial administration of brachytherapy.

Objectives:

The aim of the study was to highlight the potential role of SIRT as a treatment modality in the management of un-resectable NET liver metastases.

Methods and Results:

SIRT was performed in two carefully selected patients with un-resectable liver metastases from NET. Liver and tumour volume calculations were performed on pre-treatment CT scans. Volumetry was performed both subjectively by an experienced interventional radiologist and objectively by computed tomography (CT) volumetry using radiologic image analysis software (Image J). Fractional tumour and liver flow characteristics and lung shunt fractions were determined using hepatic arterial Tc-99m MAA imaging.

Radioactive ⁹⁰Y resin microspheres were administered through a percutaneous hepatic artery catheter. Patients were monitored prospectively, and the response to treatment was measured by using cancer markers, tumour size on CT and PET/CT imaging.

Symptomatic response was observed in both patients. Radiologic response was observed by decrease in tumour volume on follow-up CT and decrease in intensity of FDG uptake on PET/CT. There were no major complications post SIRT.

Conclusions:

SIRT represents a promising treatment modality for controlling liver metastases from NET. Careful selection of patients through the combined expertise of a well-integrated multi-disciplinary team involving interventional radiology, nuclear medicine, medical oncology, surgical oncology, medical physics, and radiation oncology, is the foundation behind a successful program in order to maximize therapeutic efficacy and reduce the potential for adverse effects.

P031 A Case of Lung Carcinoid Metastasizing to the Pleura and Spleen

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A 44 year old woman presented with chest pain and a well circumscribed left upper lobe opacity on chest x-ray. Chest CT confirmed a tumour and a PET scan identified no metastases. Thoracotomy performed in December 2000 revealed a smooth, 3 cm, rounded tumour that was histologically identified as typical carcinoid. Excision margins were clear and the patient was discharged from the chest clinic 5 years later.

In early 2009 our patient re-presented with left-sided pleuritic chest pain. On direct questioning, she had felt wheezy, sweaty and nauseated for the preceding 4 months. Chest CT showed multiple enhancing pleural-based lesions, most likely signifying recurrence of her carcinoid. Interestingly, a new 4.7 cm splenic lesion was also identified. A gut hormone profile demonstrated a markedly raised chromogranin A: >1000 pmol/l (ref range 0-60) and B: 348 pmol/l (ref range 0-160). 24 hour urine 5HIAA was also elevated at 279 umol (ref range 0-40).

⁶⁸Gallium-Dotatate PET/CT scanning showed avid tracer uptake from the pleural lesions but none from the splenic mass. A biopsy of the splenic lesion was performed and histologically identified as a metastatic low grade neuroendocrine carcinoma. WHO criteria were fulfilled for typical carcinoid. Our patient now waits funding for lutetium therapy and is being considered for splenectomy.

Splenic metastases from lung carcinoid are very rare. To our knowledge, there is one Japanese case report in the literature which has also described this (Takada et al. 1998). Metastatic spread to the pleura is also very unusual with three cases described in the literature to date (Klee et al. 2008).

We have described a case of bronchial carcinoid that has metastasized to potentially two (one biopsy-proven) rare sites. This presents new therapeutic challenges.

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P032 Lomustine plus 5FU or Capecitabine: a single centre experience of a practical and effective regimen in treatment of neuroendocrine cancers.

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Streptozocin has remained a backbone of the chemotherapy treatment of neuroendocrine cancers for decades, often in combination with 5-fluorouracil (5FU). However, issues of toxicity, supply and the requirement for intravenous administration have spurred the search for alternative regimens. The oral alkylating agent Lomustine (CCNU) has been combined with 5FU in a regimen developed at St Bartholomew's hospital with evidence of tolerability and efficacy (Ref).

Over the past 8 years we have treated 27 patients with a lomustine based regimen in our centre. Initially this was in combination with 5FU/folinic acid (11 patients) but latterly a completely oral regimen with Capecitabine was used (20 patients; 4 patients retreated with oral regimen). The site of the neuroendocrine cancers in these patients were; 9 pancreatic; 10 small intestine; 3 rectal; 2 unknown primary; 1 renal; 2 paraganglioma

Toxicity with these regimens has been modest. Mucositis, diarrhoea and hand-foot syndrome has rarely been problematic. Bone marrow toxicity (predominantly myelosuppression and thrombocytopenia) has mainly resulted in reduced dose intensity (through treatment delays) rather than neutropenic fever or sepsis.

Responses were seen particularly in pancreatic NET and paraganglioma. Several patients received multiple courses of treatment with symptomatic and radiological benefit.

Full data on toxicity, response and survival will be presented.

P033 Correlation of Radiological findings with Clinical Course in Patients with Metastasising Carcinoid Disease

M. Banks, G Poston, D Cuthbertson, H Wieshmann

Carcinoids tumors account for 0.7% of all malignancies. University Hospital Aintree is a tertiary referral centre for patients with Carcinoid disease and neuroendocrine tumors. Some patients with carcinoid disease and radiological findings indicating liver and/or mesenteric nodal disease were followed up for more than 5 years. However the patients remained relatively symptom free for more than 5 years despite persistent abnormal radiological findings. Awareness of this discrepancy is of great importance in the radiology follow up and management plan of patients with carcinoid tumors. This pictorial review will illustrate the discordance of radiological appearances, chromogranin levels, biochemical findings and the clinical course in several patients with metastatic carcinoid tumors.

P034 Somatostatin Receptor Scintigraphy and Subsequent Radiolabelled Therapy in Neuroendocrine Tumours: a single institution experience

Metcalfe R L, David J, Lee K, Valle J W

Background

Somatostatin receptor scintigraphy (SRS) improves the sensitivity and specificity of conventional radiographic investigations in neuroendocrine tumours. In patients with positive SRS, radiolabelled somatostatin analogues can be administered therapeutically.

Concerns have been raised that SRS used inappropriately does not provide clinically useful information. We audited the use of MIBG and somatostatin scintigraphy in patients with neuroendocrine tumours at our institution.

Method

A list was obtained from the radiology database for all the SRS scans performed on patients with neuroendocrine tumours at the Christie NHS Foundation Trust between February 2007 and October 2008. The case notes and request cards were reviewed, specifically assessing i) whether the SRS provided additional information in the management and ii) what proportion of patients with positive SRS proceeded to have radiolabelled therapy.

Results

82 SRS scans (60 Octreotide, 22 MIBG) were performed during this period on patients with neuroendocrine carcinomas. Disease was avid on 34/60 Octreotide scans and 11/22 MIBG scans.

SRS added information above the conventional radiography performed in 96% of cases: informing decision on radiolabelled therapy (78%); identifying the extent of disease (51%); excluding post operative recurrence (18%); confirming the diagnosis with no histology (6%); and identifying an unknown primary site (1%).

79/82 (96%) of the patients undergoing SRS had a previous CT for comparison. 14/79 had no disease on the CT. 2 of these 14 (14%) with normal CT imaging had positive SRS. The extent of disease was equal on CT and SRS in 43%, greater on CT in 34% and greater on SRS in 23%.

Of the patients with avid SRS scans only 7% (n=3) during this period proceeded to radiolabelled therapy. The specific clinical question on 30% (n=25) of the request cards was to assess the suitability for radiolabelled therapy.

Conclusions

The use of SRS added to the clinical information in 96% of scans performed. CT and SRS imaging should continue to be performed at the clinician's discretion. The reasons for the lack of provision of radiolabelled therapy needs to be assessed.

P035 5 years of the Cardiff NET MDT – are we making a difference?

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Background: Neuroendocrine tumours (NETs) are complex tumours which require management in a multidisciplinary team (MDT). The Cardiff NET MDT was established in early 2005 and accepts referrals from all areas in South East Wales (population 1.5 million). Here we review our experience of the first 5 years of this service.

Results: Since inception, over 300 cases have been reviewed (n=74 2005/6, n= 74 2006/7, n=64 2007/8, n=74 2008/9, n=28 first half 2009/10) including 173 new referrals (n=51 2005/6, n=33 2006/7, n=30 2007/8, n=40 2008/9, n=19 first half of 2009/10). 54% of cases were brought to the MDT by endocrinologists at the University Hospital of Wales (UHW), 33% by UHW surgeons, 7% by surgeons outside UHW, 4% by oncologists and 12% others. The mean age at diagnosis was 53.5 years (range 16-78) with a slight female preponderance (53%). Primary tumour sites comprised: midgut 36%, unknown primary (or information not available) 35%, pancreas (including MEN-1) 13%, stomach/duodenum 3%, rectum 3% and extra-intestinal 10%. Only 31% patients had evidence of distant (liver) metastases at the time of diagnosis. Imaging was undertaken in 92.5% (CT 75.5%, MRI 18.6%, USS 3.1%, nuclear imaging 29.6%) with most scans performed at UHW, including all nuclear imaging (with SPECT/CT co-localisation). Standardisation of histological reporting has improved following the introduction of All Wales NET guidelines (2008), incorporating the Royal College of Pathologists standards. A change in management was recommended for a significant number of patients, with 20 patients having undergone further surgery, 7 not already established on somatostatin analogues being commenced on therapy, 10 having received chemotherapy, 3 hepatic artery embolisation, 1 SIRT therapy and 3 radiolabelled treatments (one ⁹⁰Y-DOTATOC, two ¹³¹I-MIBG) in the last 2 years alone.

Conclusions: Referral numbers appear to have reached steady state with the number of new cases in keeping with the known incidence of NETs in the general population. Tumours would appear to be sent for review at early disease stage. Standardisation of histological reporting has improved and management is changed in a substantial majority.

P036 Adrenal adenoma with myelolipomatous metaplasia, giving a false positive FDG PET scan, in a patient with adenocarcinoma of the lung: case report

Ben Whitelaw, Matthew Allum, Nicola Mulholland, Pauline Kane, Salvador Diaz-Cano , Klaus-Martin Schulte, Simon Aylwin

Background

Adrenal masses detected in the context of primary lung cancer must be characterised optimally. Although benign adrenal adenomas are common, the adrenal gland is a common site for metastatic spread of lung cancer and the presence of a confirmed metastasis will affect management. Recent publications have suggested combined CT and FDG PET can achieve a sensitivity of 100% and specificity of 99% for detection of malignancy.

Case Study

A 62 year old lady was incidentally found to have a left sided adrenal mass on MRI scan of the lumbar spine to investigate sensory symptoms affecting the right leg. Clinical assessment revealed no endocrinopathy. A dedicated adrenal CT scan then showed a 38 x 28mm left sided adrenal lesion, with increased attenuation atypical for an adenoma. Pre-contrast attenuation was 30 HU, venous phase 57HU, delayed phase 42HU, with absolute wash out value of 55%. Biochemistry suggested low grade autonomous cortisol secretion. The patient was planned for adrenal surgery but found to have a left lower lobe lung lesion on chest x-ray during pre-operative assessment.

Wedge resection of the left lower lobe was performed and histology demonstrated primary adenocarcinoma of the lung. An FDG PET scan was then done which showed intense uptake in the left adrenal. Combined second stage lobectomy together with left adrenalectomy was then performed. There was no pathological evidence of residual adenocarcinoma and no lymph node involvement. Histology of the left adrenal gland demonstrated an adrenal cortical adenoma with focal myelolipomatous metaplasia. The patient made a good recovery and remains well 12 months later.

Discussion

Here we describe a left adrenal lesion, strongly positive on pre-operative FDG PET, subsequently confirmed to be a benign adrenal cortical adenoma. Previous publications have claimed a very high level of sensitivity and specificity for radiological analysis of possible metastatic adrenal lesions. Reports of previous false positive FDG PET scans have been attributed to pheochromocytoma or presumed adenoma lesions on which histology is unavailable. This case report demonstrates focal myelolipomatous metaplasia in an adrenal adenoma which may account for the intense uptake on FDG PET scan.

P037 UKINETS 2009 Abstract Submission - Magnetic Resonance Imaging and Diffusion Weighted Imaging in Evaluation of Pancreatic Neuroendocrine Tumours

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Abstract:

Pancreatic neuroendocrine tumours (PNETs) are rare tumours arising from pancreatic islet cells. The majority are hyperfunctioning and present early due to an associated clinical syndrome. 15-30% are non-functioning and are detected incidentally, with non-specific symptoms or due to mass effect. Cross-sectional imaging plays an important role in localisation of the primary lesion, identifying sites of metastatic disease and assessing treatment response. PNET localisation can be difficult and may require a combination of different imaging modalities with the sensitivity for detection of small tumours being dependent on optimal technique. Although there is no established consensus on the most efficient imaging pathway, computed tomography (CT) is generally the primary modality with magnetic resonance imaging (MRI) currently used as an adjunct to localise clinically or biochemically evident lesions not demonstrated on triple phase multi-detector CT (MDCT).

We will review and illustrate the role of imaging in diagnosis and localisation of PNETs highlighting the pitfalls and diagnostic performance of different modalities. Particular emphasis will be placed on MRI and the use of diffusion-weighted imaging (DWI). We will highlight cases from our practice where lesions were only detected on DWI or where this sequence conclusively increased lesion conspicuity and reader confidence.

P038 An aggressive phenotype in MEN 1: requirement for more frequent monitoring?

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Mr SC is an 18-year old gentleman with MEN 1 with a heterozygous germline mutation at the p.W341X locus of the MEN 1 gene. He was originally referred, aged 16, when he was noted to have mild hyperparathyroidism and raised chromogranin levels (90pmol/L (NR <60)). His other gut and pituitary hormones were normal. Abdominal CT scan revealed a 3cm lymph node between the pancreas and lesser curve of the stomach, which showed increased activity on an octreotide scan. Additional lesions were noted in the pancreatic neck and head, measuring 15mm and 18mm respectively, and a submucosal lesion in the lesser curve of the stomach. Following an endoscopic ultrasound, a coeliac lymph node biopsy revealed a low-grade neuroendocrine tumour. Within 6 months, Mr SC developed symptoms consistent with hypoglycaemia confirmed on a 72h fast. Angiography with calcium stimulation and venous sampling revealed blushes in the tail/body and head of the pancreas after injection of the splenic (SA) and dorsopancreatic (DPA) arteries respectively with a diagnostic rise in insulin (SA: baseline 4.8 to peak 48 mU/L and DPA: baseline 6.4 to 243 mU/L) confirming that both pancreatic lesions were functional. The patient underwent a laparoscopic enucleation of both pancreatic lesions, in addition to a gastric lesion wedge resection and gastric lymph node removal. On histology, both pancreatic lesions were consistent with insulinomas and the gastric wedge resection and adjacent lymph node confirmed a primary gastric neuroendocrine tumour. His hypoglycaemic symptoms have completely resolved following surgery. His father (the index case) presented at age 38 years, in 2005, with recurrent hyperparathyroidism when the diagnosis of MEN 1 was confirmed after genetic testing. Within a year of diagnosis, in addition to a completion parathyroidectomy, he had undergone hypophysectomy for both aggressive Cushing's disease and microprolactinoma, and also has multiple pancreatic lesions including a functional gastrinoma indicating a fairly aggressive phenotype. He now has evidence of recurrent Cushing's disease and also symptoms of hypoglycaemia awaiting investigation. Although, there are no clear genotype/phenotype correlations in MEN 1, this case highlights that more aggressive screening may be appropriate in young patients with MEN 1 whose first-degree relatives have multiple and aggressive endocrine tumours.

P039 Severe hypergastrinaemia with marked symptomatic rugal hypertrophy in a patient with MEN 1

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This 54 year old female who has MEN 1 with a confirmed mutation in the MEN gene, presented in 1990 with primary hyperparathyroidism and underwent a two-gland parathyroidectomy with a further completion parathyroidectomy in 1998 for recurrent hypercalcaemia. In 1990, she was also diagnosed with a gastrinoma (co-secreting insulin) treated with a proton-pump inhibitor. In 2005, CTscan, revealed a 2.8cm lesion in the pancreatic head and two duodenal lesions (7.4mm and 7mm), consistent with neuroendocrine tumours (NET) with no change since 2003. Octreotide scan confirmed increased uptake in the head of the pancreas consistent with NET. Visceral angiography with calcium stimulation and venous sampling in 2005 confirmed a rise of gastrin in superior mesenteric artery (SMA) and dorsal pancreatic artery (DPA) corresponding the lesions seen on CT scan (Basal gastrin 8000 to peak in SMA 23,700pmol/L and peak in DPA 28,700pmol/l) and a rise in insulin in the SMA and DPA (SMA:Basal insulin 9.0 to peak 46iu/L and DPA:basal of 66 to peak 82iu/L). In 2006, she developed microcytic anaemia and OGD and Colonoscopy were normal apart from moderate rugal hypertrophic gastritis with neuroendocrine cell hyperplasia on biopsy. The microcytic anaemia was presumed to be secondary to uterine fibroids and menorrhagia which improved on Norethisterone. Her current medication includes Omeprazole 40mg bd, Thyroxine 50mcg od, 1-Alfacalcidol 0.75mcg od and Loperamide prn. On review this year, she was complaining of a significant increase in gastrointestinal symptoms with nausea, abdominal discomfort, intermittent diarrhoea and intermittent dysphagia. Abdominal MRI scan revealed that the enhancing lesion within the pancreatic head had markedly increased in size to 4.7 cm with no change in the two lesions in the duodenal wall. The gastric rugal hypertrophy had progressed significantly with the stomach lumen now almost totally obliterated. This lady is awaiting a Gallium-DOTOTATE PET scan and Barium meal. In view of the marked progression of the pancreatic head lesion, rugal hypertrophy and symptomatology, in addition to a trial of octreotide therapy, we feel that this lady would benefit from surgical removal of pancreatic head and duodenal lesions as a debulking procedure and to reduce her hypergastrinaemia which should ameliorate her symptoms.

P040 Removal of a pancreatic lesion for symptomatic relief in a patient with MEN 1

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This 30 year old gentleman with MEN 1, confirmed on genetic testing, was diagnosed after he developed primary hyperparathyroidism for which he had a two-gland parathyroidectomy in 2008 (aged 29 years). He has remained normocalcaemic with normal PTH post operatively. Abdominal investigations revealed multiple insulinomas and gastrinomas within the pancreas. In 2008, abdominal CT and MRI scans revealed multiple lesions within the pancreas (2-3 in head (largest 14 mm), 1 in neck, 3 in tail (largest 3.3 cm)), consistent with neuroendocrine tumours (NETs). Three were seen on angiography: one in head was supplied by anterosuperior pancreaticoduodenal artery; in neck by branch of dorsopancreatic artery (DPA) and one in tail by splenic Artery (SA); Calcium stimulation test and venous sampling showed increase insulin x12 from SA, x2 from IPDA, GDA, SMA and x1.6 from DPA but none from hepatic artery suggesting all three angiographic lesions were secreting insulin. Indium octreotide scan showed increased uptake probably in pancreatic head. He underwent enucleation of the NETs in pancreatic tail and head in February 2009. The tail lesions confirmed low grade NET but no positive histology from excised lesion in head. However, post operatively he remained very symptomatic off a proton pump inhibitor (PPI) and also had continued episodes of hypoglycaemia. He was intolerant of Diazoxide. On post-operative 3-day fast, he became hypoglycaemic at 28h: glucose 2.0 mmol/L, insulin 6.8 mU/, C-Peptide at 523 pmol/L. Fasting gut hormones showed raised chromogranin A and B, gastrin 129pmol/L (NR <40), glucagon 70 pmol/L (NR <50). Repeat abdominal CTscan showed at least 2 lesions in pancreatic head and persistent 3.5 cm lesion in tail of pancreas. As the major source of insulin appeared to be secreted from the lesion in pancreatic tail which could be removed laparoscopically and may improve his QOL and as excision of the lesion in pancreatic head would require an open procedure, the patient underwent a laparoscopic distal pancreatectomy. Histology confirmed low grade NET (>50% cells stained for insulin). This has caused complete resolution of his hypoglycaemic symptoms with dramatic improvement to his QOL-he feels better that he has done for more than 10 years. However, he still requires a PPI without which he becomes very symptomatic.