



ABSTRACT BOOK

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OC001 Treatment Outcome and Prognostic Factors of Gastric Carcinoid Tumors.

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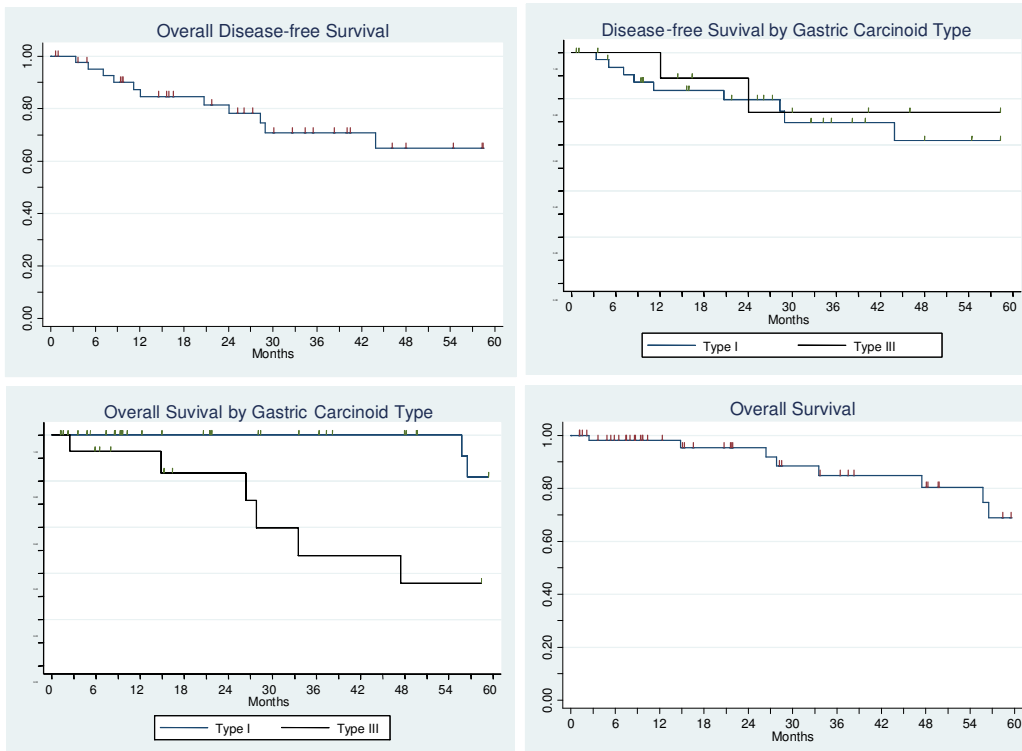
Introduction: Gastric Carcinoids (GC) are considered relatively rare tumors with peculiar features which differentiate them from other type of carcinoids. However, the precise natural history and surgical outcome of GC are not fully understood. The objective of this study is to clarify the clinicopathologic features of GC and evaluate prognostic factors predicting survival.

Methods: Review of patients treated for GC tumors at our institution from 1997-2008. Overall and disease-free survival were calculated using the Kaplan-Meier method and the significance of prognostic variables was evaluated by log-rank and Cox regression analyses.

Results: 75 patients, mean age 60 years, and 61% female. GC type I: 52 (69%), type II: 3 (3%) and type III: 20 (27%). Multifocality was observed in 44% of type I tumors vs 0% in type II and 12% in type III ($p=0.01$). Metastases to lymph nodes or liver at time of diagnosis was found in 12%, 33% and 40% of type I, II and III GC respectively ($p=0.01$). Age ($p=0.04$), personal history of other type of cancer ($p<0.01$), tumor size ($p=0.03$), and tumor stage ($p=0.04$) were significantly associated with the type of GC tumor.

The median disease-free survival (DFS) for 46 patients who underwent curative procedures was 88 months with a 5-year DFS rate of 65%. Five year OS was negatively impacted by type III GC, age > 60 years, and advanced stage. In multivariate analysis, only type of GC affected 5-year overall survival (81% for type I vs. 36% for type III). The median overall survival rate for type I and type III GC was 100 months and 34 months, respectively ($p<0.001$).

Conclusions: Our analysis confirms the heterogeneous tumor biology of GC tumors. Type I tumors tend to be multifocal and indolent, however they can acquire malignant potential as highlighted by our data. Overall survival is significantly shorter among patients with type III vs. type I GC.



OC002 Adenosine Receptor Signal Pathways in Neuroendocrine Tumours

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Background

Neuroendocrine tumors (NETs) of GI tract are a heterogeneous group of neoplasms that secrete peptides and amines. Small bowel NETs originate from enterochromaffin (EC) cells and secrete Chromogranin A (CgA) and serotonin (5-HT). NETs are highly vascular, a reflection of increased tumour related angiogenesis. Adenosine, the major regulator of angiogenesis, is released by enhanced degradation of ATP, during cellular stress, damage and hypoxia.

Aim & Objective

To investigate the expression and function of adenosine receptors (AR) in the human NET cell lines BON-1 (pancreatic) and KRJ-1 (intestinal-EC cell) and to identify AR expression in archival material from NET patients.

Methodology & Results

In vitro: RT-PCR coupled with sequencing showed that KRJ-1 cells expressed all four AR: A1, A2a, A2b and A3; a similar pattern of expression was seen in the BON-1 cells although the A3R transcript was barely detectable. In both cell lines, cAMP stimulation data using selective AR agonists and antagonists showed that the predominant receptors were of the A2 (both A2a and A2b) subtypes. The ED₅₀ values for adenosine in both cell lines was between 5×10^{-7} and 10^{-6} M with a 3-15 fold increase in cAMP levels ($P < 0.01$). The stable AR agonist NECA and the A2aR selective agonist CGS21680 stimulated cell proliferation (MTS assay) by 20-30% at 10^{-5} M agonist ($P < 0.05$). In BON-1 cells adenosine and NECA also stimulated a 2-fold ($P < 0.05$) secretion in CgA (as measured by radioimmunoassay), with ED₅₀ values of respectively 5×10^{-6} and 10^{-7} M.

Ex vivo: 18 archival human NET histopathological tissue samples (pancreas, small bowel and appendix) were obtained & immunostained for AR. For the A2bR strong labelling was seen in 4/4 appendiceal tumours, 4/4 pancreatic tumours and 4/9 intestinal tumours and for the A2aR 15/15 tumours were strongly positive. There was very weak or no staining for the A1 and A3 receptors

Summary

Our data suggest that NETs express predominantly the A2a and A2b receptors. Activation of these receptors leads to increased proliferation and secretion of CgA. Targeting adenosine signal pathways may thus be useful in the therapeutic management of neuroendocrine tumours.

OC003 Somatostatin producing cells are significantly decreased in insulinoma islets of Multiple Endocrine Neoplasia Type 1 (MEN1) knockout mice: implication for pancreatic proliferation rates.

Jeshmi Jeyabalan, Anita A. C. Reed, Gerard V. Walls, Brian Harding and Rajesh V. Thakker

D cells comprise 3 to 10% of the human endocrine pancreas and secrete somatostatin, which inhibits cell proliferation and hormone secretion. Pancreatic tumours secreting somatostatin are associated with the somatostatinoma syndrome, which is characterised by hyperglycaemia, cholelithiasis, a low acid output and anaemia. We have examined for the presence of somatostatin-secreting cells in pancreata from a multiple endocrine neoplastic type 1 (MEN1) knockout mouse model, which develops pancreatic endocrine tumours that are mostly insulinomas, as well as parathyroid and pituitary tumours. Mice were kept in accordance with UK Home Office welfare guidelines and project licence restrictions. In order to assess proliferation rates *in vivo*, drinking water containing BrdU at 1mg/ml, which becomes incorporated into the DNA of dividing cells, was given to 19-21 month old wild-type (+/+) and *Men1* (+/-) littermates for 4 weeks. Pancreatic sections were immunofluorescently labelled with DAPI, somatostatin and BrdU, and 6 islets or pancreatic endocrine tumours from each of 4 animals per genotype were analysed to determine the percent of somatostatin and BrdU co-positive cells. The pancreatic islets of wild-type (+/+) mice contained significantly ($p < 0.001$) more somatostatin-positive cells than those in the islet cell tumours of *Men1*+/- mice ($18\% \pm 2.5\%$ versus $3.5\% \pm 1.5\%$, mean \pm SEM). However, the somatostatin-containing cells in the islet cell tumours of the *Men1*+/- mice had a significantly ($p < 0.002$) higher proliferation rate when compared to those in pancreatic islets of wild-type (+/+) mice ($0.57\% \pm 0.25\%$ per day versus $0.01\% \pm 0.01\%$). Thus, our findings indicate that somatostatin-secreting cells (D-cells) comprise ~18% of the normal mouse endocrine pancreas. However, in *Men1*+/- pancreatic endocrine tumours, somatostatin-containing cells, which have a higher proliferation rate, comprise less than 5% of the cells, and the accompanying reduction in somatostatin secretion may contribute to the observed higher proliferation rate in these tumours.

OC004 Efficacy of standard activity of ¹³¹I-MIBG therapy in patients with disseminated neuroendocrine tumours

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The aim of the study was to evaluate the response of standard activity of ¹³¹I-meta-iodobenzylguanidine(MIBG) in metastatic neuroendocrine tumours (NET) looking at symptomatic response, tumour size as assessed by CT and relevant plasma tumour markers.

A retrospective review of patients who had undergone ¹³¹I-MIBG between March 2001 and December 2006 was carried out. Clinical data was collected by case note review including symptomatic checklist forms. A total of 38 patients were identified.

Of the 38 patients treated, 25 were male and 13 female. The median age was 65.0 (range 38 to 86). The distribution of NETs was as follows: 27 patients had gastrointestinal carcinoid tumours, 6 patients' pancreatic neuroendocrine tumour, 3 phaeochromocytoma, 1 bronchial carcinoid and 1 malignant paraganglioma. Histological grade was available in 22/38 patients; 8 with low grade NET, 12 with intermediate grade NET and 2 with high grade NET.

We were able to evaluate symptomatic response in all 38 patients. 15 patients had improved symptoms, 19 had no improvement in their symptoms, whilst 4 patients were asymptomatic prior to and after therapy. In those with a symptomatic response, the mean overall survival was 62.25 months compared to those without a symptomatic response of 30.4 months ($p < .0001$).

CT response was evaluated in 37/38 patients. In those with stable disease, the mean overall survival was 45.1 months compared with progressive disease of 25.1 months. The difference between these two groups were significant with $p=0.01$.

The hormonal response to therapy was available in 20/38 patients. 10 patients had increased hormone levels post therapy, 3 patients had decreased hormone levels and 7 had stable hormone levels. There was no difference in the mean overall survival for the 3 groups of 29.5 months, 28 months and 27 months respectively.

Only 2 patients developed a significant haematological toxicity (1 with a grade 3 thrombocytopenia and 1 with a grade 3 pancytopenia).

We can conclude from this data that ¹³¹I-MIBG is well tolerated and that symptomatic response to treatment is a significant predictor of overall survival.

OC005 Review of outcomes of patients with advanced neuroendocrine carcinomas treated with Interferon therapy: a single-institution experience.

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Background: Interferon (IFN) is a treatment option for patients with advanced (non-resectable) neuroendocrine tumours (NETs). In this retrospective analysis, we evaluated the effect of IFN on biochemical markers, survival and radiological progression at our institution.

Method: Individual case notes of all patients with NETs prescribed IFN between January 2001 and December 2007 identified from the pharmacy database were reviewed.

Results: Notes were available for 87 of 90 patients identified (median age 59, range 18 – 83 years; males/females (n) 45/42). The most common sites of primary tumour were the small bowel, pancreas and unknown primary in 24%, 23% and 25% respectively. Ninety-five percent of patients had metastatic disease and 57% of cases had biochemically functional tumours. IFN prescribing was in keeping with institutional guidelines in 84/87 (96.6%) of cases. Although most patients tolerated IFN well, 4 patients had a dose reduction and 34 patients (39%) had to discontinue treatment due to side effects.

5-HIAA response was assessable in 37/50 patients: in 5 (10%) patients 5-HIAA levels doubled despite medication, 2 (4%) patients had <100 and >50% increase, 9 (18%) patients had ≤50% increase, 16 (32%) patients ≤50% decrease (5 of these patients also received a somatostatin analogue – SSA), and 5 (10%) patients showed a ≥50% decrease of 5-HIAA (all also received SSA). Other biochemical markers were not assessable as serial results were not available.

There appears to be improved time-to-progression in patients treated with IFN and another treatment modality simultaneously (median 23.2 months), compared with IFN alone (median 11.5 months, p=0.048). In addition patients who received somatostatin analogues at any point of their treatment in addition to anti-tumour treatments (median 40.0 months) appear to survive longer compared with anti-tumour treatments alone (median 27.8 months, p=0.03).

Conclusion: IFN prescribing was in keeping with institutional guidelines. Formal protocols to include collection of additional biochemical data (e.g. chromogranins A/B), symptoms and quality of life should be used routinely for therapies in this patient group.

In order to demonstrate an effect on survival and time-to-progression, a phase III study is required with biomarker studies to determine patient sub-groups most likely to benefit from treatment.

P001 Assessment of in vivo proliferation rates in insulinomas of Multiple Endocrine Neoplasia Type 1 (MEN1) knockout mice: implications for evaluating effectiveness of future treatments.

Gerard V. Walls, Anita A. C. Reed, Brian Harding, Jeshmi Jeyabalan and Rajesh V. Thakker.

Pancreatic endocrine tumours (PETs) have a low proliferation index and this partially accounts for their lack of response to chemotherapy. The assessment of proliferation rates relies largely on the use of markers such as Ki67 in patients, and uptake of DNA nucleotide precursors such as tritiated thymidine or 5-bromo-2-deoxyuridine (BrdU) in animals. Amongst these, BrdU is recognised to be the most reliable marker of cell proliferation as it allows the substitution of an endogenous DNA base, thymidine, with the BrdU analogue, ensuring specific labelling during S-phase of only the dividing cells. We have therefore used continuous long-term BrdU labelling to assess proliferation rates of PETs in a multiple endocrine neoplasia type 1 (MEN1) knockout mouse (+/-) model, which develops PETs that are predominantly insulinomas. Mice were kept in accordance with UK Home Office welfare guidelines and project licence restrictions. Drinking water containing BrdU at 1mg/ml was given to wild-type (+/+) and *Men1* (+/-) littermates for 1 to 12 weeks. Pancreatic sections were immunofluorescently labelled with DAPI, insulin and BrdU, and 6 islets or insulinomas from each of 4 animals per genotype were analyzed to determine the percent of BrdU-positive cells. The mean (\pm SEM) proliferation rate of normal beta-cells in wild-type (+/+) mice was 0.075% (\pm 0.010%) per day. In contrast, the mean proliferation rate of insulinoma cells in the *Men1* (+/-) mice was significantly ($p < 0.001$) higher at 0.323% (\pm 0.031%) per day. These respective proliferation rates in the wild-type (+/+) and *Men1* (+/-) mice, that had received BrdU for 1, 4, 8 and 12 weeks, were similar. Thus, our studies have established a method to measure the *in vivo* proliferation rates of insulinomas in *Men1* +/- mice, and this opens the way to assess the effectiveness of new therapies in reducing the growth of pancreatic endocrine tumours.

P002 Clinical Relevance of Insulin Growth Factor-1 Receptor(IGF1-R) Expression Scores in Neuroendocrine Tumors

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Introduction: IGF1-R overexpression is known to promote tumor progression in a variety of malignancies and is associated with reduced patient survival. Expression of IGF1-R and its clinical relevance in neuroendocrine tumors (NETs) is not yet well understood. In this study we investigated the relationship between tumor IGF1-R expression levels and clinico-pathologic characteristics.

Methods: Archival tumor sections from 32 bronchial(Br)and 28 gastrointestinal (GI) NETs were immunostained for IGF1-R. For each case pathology was reviewed and immunohistochemical expression of IGF1-R was quantified independently by the study pathologists using H-scores (Intensity of immunostaining [1+/weak, 2+/moderate or 3+/intense] multiplied by the percentage of stained tumor cells showing that intensity; adding the 3 scores to calculate the total H-score). H-scores < 20 were considered low (IGF1-R negative) and >20 as high (IGF1-R positive). Patients' records were reviewed for relevant clinical data.

Results: Patients: F44 (73%):M16(27%), median age 64 (range: 30-83, mean: 62). Median follow-up was 5.7 years. Of 60 NETs, 32 (53%) were Br and 28% (47%) were GI. As compared to Br NETS, more GI NETs were well differentiated (96% vs 65%, $p = 0.003$), and had synchronous liver metastases at the time of surgery (57% vs 3%, $p < 0.0001$). High IGF1-R scores were observed in 22 % of Br NETs and 50 % of GI NETs ($p = 0.03$). High IGF1-R scores were seen in 59 % of the primary NETs that had synchronous metastases vs 26 % of patients with localized tumors ($p=0.03$). IGF1-R scores were not statistically correlated with age, sex, histological grade, perineural, or lymphovascular invasion ($p>0.05$). Overall survival was not statistically different between GI and Br NETs ($p=0.53$); however, GI NETs had improved 5-year overall survival than Br NETs (70% vs 61%).

Conclusions: High IGF1-R expression scores were more commonly observed in GI vs Bronchial NETs and in metastatic vs localized NETs. Larger studies are needed to confirm the validity of IGFR-1 status as an independent predictor of advanced tumor stage and origin in NETs.

P003 Plasma 5-HIAA in Monitoring the Treatment of Carcinoid Disease

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Background: Carcinoid tumours make up the majority of neuroendocrine tumours (NETs) and are predominantly derived from enterochromaffin cells. Current guidelines for the management of these tumours recommend the measurement of 5-hydroxyindole-3-acetic acid (5-HIAA) in 24-hour urine collections. However, problems associated with urine collections (i.e. inconvenience, requirement of preservatives and accuracy of collection) have prompted the investigation of fasting plasma 5-HIAA. Plasma 5-HIAA has already been shown to have equal diagnostic precision to the urine collection, and has also shown promise as a marker for monitoring carcinoid disease in a small case series. Changes in plasma 5-HIAA may relate to changes in clinical symptoms, radiological changes and treatment of patients with carcinoid disease.

Methods: Serial measurements of plasma 5-HIAA using high-performance liquid chromatography (HPLC) in 22 patients with carcinoid disease were recorded. Where possible these measurements were correlated with changes in clinical symptoms, radiological changes and initiation of treatment.

Results: In 22/29 (76 %) of instances a reduction in 5-HIAA correlated with an improvement in patients' symptoms. Conversely, in 19/29 (66 %) instances when an increase in 5-HIAA correlated with a worsening of symptoms. In 9/9 (100 %) instances when an increase in 5-HIAA of greater than 50 % was observed there was also a worsening of symptoms. A decrease in 5-HIAA of more than 25 % was observed in 11/13 (85 %) patients who were started on a somatostatin analogue. In 9/11 (82 %) of instances when disease progression was shown radiologically, an increase of 5-HIAA (from 11-579 %) was observed.

Conclusion: This study provides further support for the role of plasma 5-HIAA as a marker for monitoring carcinoid disease.

P004 Circulating Angiopoietin-2 is elevated in patients with neuroendocrine tumours and correlates with disease burden and prognosis

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Introduction: Angiogenesis is an essential process in development and growth of tumours. There are a large number of angiogenic mediators including the Angiopoietin family and vascular endothelial growth factor which play an important role in both physiological and pathological angiogenesis. This study examines serum levels of angiopoietin-1 (Ang-1) and angiopoietin-2 (Ang-2) in patients with neuroendocrine tumour compared to healthy controls.

Methods: ELISA for Angiopoietin-1 and Angiopoietin-2 was performed in 47 patients with histologically proven NETs and 44 healthy controls.

Results: Serum Ang-2 levels were significantly elevated in patients compared to controls (951 vs. 499 pg/mL, $p < 0.001$), whilst there was no significant difference in Ang-1 levels. The ratio of Ang-2: Ang-1 was significantly elevated in patients compared to controls (1.33 vs. 0.659, $p < 0.001$). Serum Ang-2 levels were significantly elevated in patients with distant metastases compared to those without metastasis ($p = 0.01$) and there was also a significant difference in Ang-2 levels and volume of liver metastases, ($p < 0.014$). Time to disease progression was worse in patients with serum Ang-2 levels > 951.1 pg/ml ($p = 0.04$).

Conclusion: Serum Ang-2 but not Ang -1 is elevated in NET patients. Ang-2 may be a useful serum marker for monitoring and assessment of prognosis in patients with NETs.

P005 Diasorin Liaison Calcitonin Assay- Our Experience

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AIM Basal calcitonin levels of 10ng/L (trigger for offering pentagastrin stimulation test-PGT) and stimulated calcitonin of 100 ng/L (trigger for therapeutic intervention) are used as a diagnostic cut-off by most laboratories investigating patients for medullary thyroid carcinoma. However, these guidelines were adopted on the basis of results from studies that used the Cisbio Immunoradiometric assay for measuring calcitonin. In the recent years, most laboratories have moved to fully automated chemiluminescent assays. Our laboratory uses the Diasorin Liaison chemiluminescent assay for measuring Calcitonin. We established our local reference ranges and assessed the validity of continuing to use the old diagnostic cut-offs

METHODS Following ethics approval, 82 healthy, euthyroid and normocalcaemic volunteers (40 female and 42 male) were recruited to obtain basal blood samples for calcitonin. 20 of the above volunteers (10 male and 10 female) also underwent the PGT. During the PGT, samples for calcitonin were collected at time points 0, 1, 2, 3, 5, and 10 minutes after 0.5 mcg/kg of pentagastrin was injected intravenously. Blood was collected into cooled plain tubes and allowed to clot. Samples were immediately centrifuged, serum stored at -20°C and assayed using the Diasorin Liaison Calcitonin assay.

RESULTS The manufacturers quote a reference range of < 5.5 ng/L for females and <18.9ng/L for males. Our study showed that the upper limit for males (22 ng/L) is similar to the manufacturer's range. However, the value for females 11.1 ng/L) is double the recommendation but is in keeping with observations made in our clinical practice and similar to the reference ranges quoted by manufacturers of most other calcitonin assays. 47.5% of men and 18.6% of women had basal levels above the old diagnostic cut-off of 10ng/L. In the PGT, women had significantly lower peaks. All except one (peak=38 ng/L) female had peak levels of less than 30. Men had higher peaks going upto 110 ng/L .

CONCLUSION In view of the above results, the old diagnostic cut-offs cannot be extrapolated to results obtained on the Diasorin Liaison assay.

P006 Dual radio-targeted therapy of neuroendocrine tumours with I-131-mIBG and Y-90-octreotate

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Radio-targeted treatment of neuroendocrine tumours (NETs) is well established, with evidence of good symptomatic response. Y-90-labelled Somatostatin analogues target tumours via the Somatostatin-subtype-2 receptors whilst I-131-mIBG is taken up by an energy and sodium dependent amine uptake process. The decision on which agent to use is based on the results of imaging with In-pentetreotide/Ga-68-DOTATATE and I-123 mIBG.

Unfortunately progression in disease size and activity can occur up to several years after initial treatment. In most cases re-imaging shows re-growth of tumour with the same characteristics as the original tumour. However we noted that in some patients, re-imaging showed no uptake of that particular agent in the recurrent tumour but uptake of a different agent. Alternatively there was disease progression whilst being treated with a particular agent. The aim of this review was to determine how often such an event occurred.

We retrospectively reviewed the case-notes of 231 patients treated with radionuclide therapy for NETs over the past 10 years. The problem was identified in 14 patients (6.1%), including 7 midgut carcinoids, 4 pancreatic NETs, 1 pancreatic gastrinoma, and 1 hindgut carcinoid.

In 13/14 patients' I-131-mIBG was the first agent used. A mean of 3.6 therapies were administered (Range 1-9). Of these 13, 6(46%) had equivalent uptake on diagnostic I-123I-mIBG and In-111-pentetreotide scans, 6(46%) had more tracer uptake on the I-123I-mIBG scan and 1(8%) had slightly more uptake on the In-111-pentetreotide scan. In the only patient treated with Y-90-octreotate first, there was equivalent uptake in the 2 diagnostic scans.

At the second course of treatments, the 13 patients who previously had I-131-mIBG, now received Y-90-labelled-somatostatin analogues. Of these, 8(62%) had better uptake on the In-111-pentetreotide, 3(23%) had equivalent uptake and 2(15%) had progressive disease on I-131-mIBG treatment. A single patient had I-131-mIBG as the second treatment, with pre-therapy imaging now showing superior uptake of tracer on I-123-mIBG.

The cause of the difference in uptake of tracer post therapy is unclear but may reflect an adaptive response of the cells exposed to a particular radio-targeted therapy or may just represent genetic variation in the make up of disseminated NETs.

P007 Intra-abdominal fibrosis in a modern cohort of patients with mid-gut carcinoid tumours – a cross-sectional survey from one centre

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Background: Fibrosis is a hallmark of mid-gut carcinoid tumour. It may manifest as desmoplastic reaction in the mesentery with the involvement of other sites, including the retroperitoneum, pleura, skin and cardiac valves. The pathogenesis of fibrosis probably involves serotonin (via the 5HT_{2B} receptor) and downstream pathways including TGF- β and CTGF. Carcinoid heart disease affects about 20% of patients in current cohorts, half of whom have significant clinical sequelae. In contrast, the prevalence and clinical significance of intra-abdominal fibrosis has been reported in few series.

Objectives and Methods: We included all patients with mid-gut carcinoid tumors and available imaging over the past 8 years. The case records were reviewed for demographic characteristics, history of small bowel obstruction and biochemical investigations. The imaging was independently reviewed for features characteristic of carcinoid. Where imaging of other sites was also available, the occurrence of extra-abdominal fibrosis was sought.

Results: In total, 32 patients were included in the study, 16 men and 16 women. Twenty-seven patients (78%) had liver metastases on imaging. Eleven patients (34%) had small-bowel thickening and one had small-bowel separation; 16 patients (50%) had evidence of mesenteric involvement, with a mass. The mass was associated with coarse calcification in 7 patients, soft-tissue stranding in 11 patients and “indrawing” of tissues in 9 patients. Five of the 16 patients had all three associated features. One further patient had soft-tissue stranding without a mass. Two patients had a “misty” mesentery and 2 patients had early retroperitoneal fibrosis. Three patients had incidental evidence of extra-abdominal fibrosis (pleural thickening). Mesenteric involvement was not correlated with gender or mean 24-hour urinary 5HIAA. Of patients with radiological fibrosis, 31% had a history of small bowel obstruction, in comparison to 7% in the group without fibrosis ($P>0.05$).

Conclusions: Intra-abdominal fibrosis can be detected radiologically in around 50% of patients with mid-gut carcinoid. This is seen more frequently in patients with previous small-bowel obstruction. Prospective studies are needed to evaluate predictors of the onset of fibrosis, correlation with fibrosis in other organs and relationship to clinical course. The effects of therapies aimed at preventing fibrosis, including somatostatin analogues and 5HT_{2B} antagonists, require prospective trials.

P008 Long-term survival in mid-gut carcinoid

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Introduction:

Mid-gut neuroendocrine tumours (NETs) include those arising in the jejunum, ileum and proximal colon. The vast majority are carcinoids. Historically, the prognosis for NET patients varied according to location and stage, and median survival rarely exceeded 5 years. We therefore analysed outcomes of mid-gut carcinoid patients managed at a single tertiary centre.

Patients and Methods:

We evaluated 151 mid-gut carcinoids from a prospective database presenting between 1989 and 2008, measuring survival, and impact of disease stage from the time of diagnosis. Survival analysis was performed using Kaplan-Meier methodology.

Results:

There were 66 (44%) males and 85(56%) females. The majority of carcinoids (63%) arose in the small bowel, with appendix 32%, and proximal colon 7%. There were 76 (50.3%) patients with loco-regional (localised or metastases to regional lymph nodes) disease and 75 (49.7%) with advanced (distant metastases) disease. Median overall survival is 135 months (95% CI 127-143 months). 5-year and 10-year absolute survival rates are 92% (SE 2.5%) and 68.5% (SE 6.6%) respectively. Age and gender had no impact on prognosis. However disease stage was highly prognostic, with mean survival of 134 months (95% CI 129-139 months) for patients with loco-regional tumours versus 103 months (95% CI 93-114 months) for those with distant disease ($P<0.0001$).

Conclusion:

Even in advanced disease, most of these patients can expect to live many years. Prolonged survival of mid-gut carcinoid may reflect not only favourable tumour biology but also the impact of multi-modality treatments. Stage of disease remains a highly significant prognostic factor.

P009 A small audit of Ki67 counts in NETs

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Introduction. The Ki67 index is an increasingly important part of the information required by clinicians from pathologists in reports of neuroendocrine tumours (NETs). Different methods may be used to assess the index. This audit was performed to check the reproducibility of one consultant pathologist's (SJJ) counts. The audit was performed in 2005 by an "Options" medical student (RB) attached to the department. The results have been presented locally and also at the North of England NET meeting.

Methods. Six NET cases were retrieved, having a range of Ki67 labelling indices as originally reported by SJJ. Cases were selected to have obvious differences between background tissue and the NET, eg liver metastases without inflammatory infiltrate. The H&E and Ki67-stained slide from each case were provided to RB, plus one-to-one training on counting technique. The cases were recounted three times by RB, with a minimum count of 1000 tumour cells per case. RB was blind to the original counts, and blinded as much as possible to his own previous counts. The mean index of his three counts was compared to the original count. RB counted with an eyepiece graticule, SJJ had not used one. Both used a cell counter.

Results. There was substantial agreement in the counts, both RB with himself and RB with SJJ's original counts, with no alterations likely to have clinical impact.

Conclusions. SJJ's Ki67 counts do seem to be reproducible.

Limitations. The study is obviously limited by: (1) small sample size; (2) only two observers; (3) the student was inexperienced at histology and cell counting; (4) any "bad habits" of SJJ could have been passed on in training and replicated by student. This has therefore not addressed accuracy, only reproducibility, but has been a useful start.

Subsequently. SJJ has obtained an eyepiece graticule for her microscope. Recent guidelines are to count 2000 cells in the area of highest labelling. Re-audit is recommended in the future.

P010 Twenty-four hour urinary 5-HIAA and survival in patients with carcinoid tumours

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Background

Twenty-four hour urinary 5-hydroxyindoleacetic acid is a well established tool used in the diagnosis and monitoring of carcinoid tumours. The aim of this study was to investigate the relationship between 24 hour urinary 5-HIAA and survival in carcinoid patients.

Materials and Methods

Samples were obtained for urine 24 hour 5-HIAA from 176 patients, age 61 (12.9) (mean[SD]). Samples were collected between January 2005 and April 2008. All patients had either histologically proven carcinoid or high clinical suspicion of disease. Twenty-eight patients died during the study period. Kaplan Meier plots were used to assess survival according to the initial sample measurements (176 samples).

Results

Data on 24 hour urinary 5-HIAA concentrations were divided into three groups: low level, intermediate level and high level at initial assessment (24 hour 5-HIAA into <20, 21-99 and >100 $\mu\text{mol}/24\text{hrs}$). Poorer survival rates were seen in the groups with highest initial 24 hour urinary 5-HIAA. This survival difference became significant ($p<0.05$) at 720 days during follow up.

Conclusions

These preliminary data suggest that a relationship exists between initial 24 hour urinary 5-HIAA concentration and survival in carcinoid patients, significant at 720 days from initial sample. Further research needs to be done to clarify this relationship.

P011 Prognostic factors in Gastroenteropancreatic Neuroendocrine Tumours

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Background: Gastroenteropancreatic neuroendocrine tumours (GEP NETs) are relatively uncommon tumours with reported incidence of 2.5-5 per 100 000 population. There is limited data available on long term clinical outcome and useful prognostic markers.

Aim: To perform a retrospective analysis to identify prognostic factors in patients who were referred to our unit from 1996 to 2008 that have subsequently died.

Methods: Data was collected from 132 patient records (63 males: 69 females) median age 58.5 (range 26-84) and a database incorporating clinical findings, histopathological features, as well as anti-tumour therapies was created. Statistical analysis was performed using GraphPad software. Detailed survival analyses of multiple parameters were performed using the Kaplan-Meier method.

Results: In the studied cohort primary tumours arose from fore-, mid-, and hindgut in 49 (37.1%), 62 (47.0%), 6 (4.5%) respectively and 15 (11.4%) patients with unknown primary sites. Distant metastases were seen in 114 (86.4%) of cases, the most frequent metastatic sites were liver in 107 (93.2%) cases, bones in 22 (19.3%) cases and lungs (12.2%) cases. The overall 5- and 10-year survival rates were 76.1% and 95.4% at 10 yr. Time to progression was significantly shorter for pancreatic compared to midgut NETs ($p < 0.05$). Survival analysis showed better clinical outcome for low grade compared to high grade tumours. No difference in survival was identified between low and intermediate grade tumours. Survival was better in patients without metastatic disease at presentation than those with metastatic disease ($p < 0.001$). There was improved survival for patients who underwent surgery at time of diagnosis compared to those that did not.

Conclusion: This study has demonstrated a number of prognostic markers including site of primary tumour, histological grade, metastatic disease at presentation which are important in management of NET.

P012 Small bowel carcinoid: the case for long term follow up.

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A 61 year old man presented in 1995 with abdominal pain and a small bowel tumour was identified. He had a resection and bypass. Histology revealed a small bowel carcinoid tumour and two further neuroendocrine tumours in the adjacent bowel wall.

All his symptoms resolved after surgery. He was followed up by the Oncology team and his urinary 5-HIAAs remained consistently normal.

10 years after his surgery, however, he started to develop watery diarrhoea which increased in frequency to seven times a day with no benefit from loperamide. He also developed abdominal pain with episodes of flushing and weight loss. At this stage his Chromogranin-A was elevated at 429pmol/l and for the first time his urinary 5-HIAA became elevated between 70-80 μ mol/24 hours.

Prompted by the elevated tumour markers he had further imaging with a CT scan which demonstrated lesions in the liver and lung together with extensive mediastinal and abdominal lymphadenopathy. These lesions were octreotide positive.

He therefore commenced treatment with Octreotide LAR with complete resolution of his symptoms. This case demonstrates the value of prolonged follow up of patients after resection of gut carcinoids, as it confirms that metastatic disease can develop even many years after the original diagnosis and apparent curative resection. Long term follow up ensured that the resultant carcinoid syndrome was correctly diagnosed and avoided the need for unnecessary investigation of his diarrhoea.

P013 Initial impact of a systematic multidisciplinary approach on the management of patients with gastroenteropancreatic neuroendocrine tumor

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A multidisciplinary approach to gastroenteropancreatic (GEP) neuroendocrine tumors (NETs) is currently advised for the optimal care of patients with GEP NET. A systematic multidisciplinary approach to GEP NETs, including regular bimonthly multidisciplinary team meetings, has been established at our Institution from May 2007. We have collected and compared the biochemistry, radiology (including endoscopy), and pathology data as well as the therapeutic strategies in the patients with GEP NET diagnosed, treated, or followed-up in our Institution since January 1993 to April 2007 (88 patients) with those from patients that came to us after the multidisciplinary approach starting (38 patients from May 2007 to August 2008). A lack of consistency in the laboratory (chromogranin A: 0%), imaging/endoscopy (54.5%), and pathology (Ki-67 and/or mitotic index: 23.9%) findings before the treatment (or the consideration for treatment) as well as in the follow-up (chromogranin A: 0%; imaging/endoscopy: 33.0%) of the patients managed before the establishment of the multidisciplinary approach was identified. These features have been at least partially reversed by the systematic multidisciplinary approach itself (chromogranin A: 10.5% pre-care, 50.0% post-care; imaging/endoscopy: 39.5% pre-care, 52.6% post-care; Ki-67 and/or mitotic index: 57.9%). Also the therapeutic management of the pre-multidisciplinary approach patients was not consistent and has been improved by the multidisciplinary approach. Despite the overall improvement of the management of GEP NET patients, further improvement needs to be achieved. This study suggests that a systematic multidisciplinary approach can provide an improvement of GEP NET patient care and should be established in all centers dealing with these tumors.

P014 Role of ¹³¹Iodine MIBG treatment in refractory, end stage, metastatic neuroendocrine tumours(NET): a single centre retrospective study

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Background: NET tumours are complex neoplasms, with metastatic disease often refractory to treatment.

Objectives: The aim of the study was to review the outcome of patients with refractory, end-stage NET treated with ¹³¹I MIBG and to evaluate our overall practice.

Methods: This was a retrospective study of patients treated with ¹³¹I MIBG between 2001 and 2007 that had been resistant to several prior therapies in a single tertiary cancer centre. Information was obtained from patient notes and electronic results system. Report of clinical symptoms and follow-up CT was used to describe treatment outcome. Biochemical and follow-up ¹²³I MIBG scan data was not used due to incomplete dataset.

Results: A total of 17 patients were treated with ¹³¹I MIBG; median age 58 years (range 39-77 years). NET sub-types included 14 carcinoid (12 gastroenteropancreatic, 1 thoracic, 1 ovary), 1 insulinoma, 1 gastrinoma and 1 pancreatic. All patients had liver metastasis and an additional site except one. All patients had pre-therapy diagnostic ¹²³I MIBG demonstrating uptake of activity above the background and liver; one was misinterpreted as a positive study. A total of 24 ¹³¹I MIBG treatments were undertaken (6 patients had more than 1 treatment dose); median dose 5.4GBq (range 4-7.5 GBq). Median time from first tertiary centre clinic presentation to commencement of palliative ¹³¹I MIBG therapy following failure to prior therapies was 145.71 weeks (range 27.86-692.71 weeks). Seven patients have since died. All except 3 treatments resulted in symptom improvement; median duration of 12 weeks (range 1–144 weeks). Post-treatment CT demonstrated 'response' in 5, stable appearance in 10, mixed response in 2 and progression in 6. 1 patient died before follow-up CT.

Conclusions: This study suggests ¹³¹I MIBG has a role in advanced end stage metastatic GEP NET tumours. Improvement/stabilisation of symptoms was seen in 88% of treatments, although often short-lived. CT data suggests ¹³¹I MIBG may have a tumour stabilising effect and hence survival benefit. Subsequent review of practice has resulted in implementation of a defined protocol for systematic follow-up of patients with mandatory repeat imaging review pre-therapy by a specialist radiologist to avoid unnecessary treatment exposure.

P015 A case of Familial Paraganglionoma

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A 32 year-old Albanian restaurant owner presented to Urology clinic with a two-year history of headache, palpitations, anxiety and sweating episodes on voiding. He had no significant past medical or family history. He was not taking any medication.

Abdominal CT scan confirmed a bladder mass and normal suprarenal glands. Cystoscopy showed an extrinsic bladder lesion.

He was found to be hypertensive, 24 hour urinary free catecholamine estimations demonstrated markedly elevated noradrenaline excretion. Iodine 123 MIBG scan was reported as normal with physiological uptake of tracer in bladder only. However, from the clinical findings, a diagnosis of bladder pheochromocytoma was thought to be most likely. Pre-operative fluid repletion and alpha and beta-blockade was followed by uneventful partial cystectomy.

Histology showed typical appearance of pheochromocytoma. Immunohistochemical staining revealed strong positivity for neuroendocrine markers (CD56, Chromogranin, Synaptophysin). Post-operative 24 hour urine collections showed normalisation of his noradrenaline levels.

In view of his young age and extra-adrenal location of the tumour he underwent genetic screening and a pathogenic deletion of exon 1 of the SDHB gene was detected by MLPA analysis which has been confirmed by long range PCR.

This case highlights the importance of genetic screening of patients with pheochromocytoma, especially those who are young and/or have extra-adrenal disease. SDHB mutations are associated with a familial paraganglionoma syndrome and are characterized by malignant disease and extra-adrenal pheochromocytoma. Prevalence, penetrance and clinical characteristics of patients carrying point mutations have been relatively well studied, but less is known regarding patients with gross deletions. Recent publications suggest that SDHB exon 1 deletion are associated with abdominal presentations and younger age of onset.

As there is a high chance of malignancy and recurrence, lifelong follow-up is necessary. More than one screening modality is essential as metastases are non-secretory in about half of cases.

This patient has a young son aged five. Ethical and practical issues regarding whether and when genetic screening should be offered will be discussed. Penetrance is variable and there is no prophylactic procedure available to prevent disease occurrence, however incidence has been documented as young as 6 years of age.

P016 Neuroendocrine tumour in the Meckel's Diverticulum, Is Diverticulectomy enough?

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Introduction: Meckel's Diverticulum is the most common true diverticulum in the GI tract. Embryologically it arises from the patent vitelline duct which normally connects the primitive gut to the yolk sac and fails to obliterate around the seventh or eighth week of gestation. The vast majority of Meckel's diverticulum are asymptomatic and found incidentally during surgery. Neuroendocrine tumours (NETs) are derived from diffuse neuroendocrine system which is made up of peptide and amine producing cells with different hormonal profile depending on their site of origin. Tumours are associated with 3-4% of Meckel's diverticulum and up to a third are neuroendocrine tumours.

Aims and Methods: The aim of our study was to assess the necessity of additional treatment in patients with NET located in Meckel's diverticulum who underwent diverticulectomy. Between 2003 and 2008 three patients (Caucasian males, median age: 48 years) with meckel's diverticulum and neuroendocrine tumour were referred. Their notes were reviewed as were scans and histology.

Result: All three patients were clinically suspected to have acute appendicitis at presentation. In the first patient tumour was found incidentally in the diverticulectomy specimen; in the other two patients tumour was found by the surgeon at laparotomy and both underwent small bowel, mesenteric and local lymph node resection. The histology of the resected samples was well differentiated of low grade (proliferation index Ki 67 < 2%) neuroendocrine tumour. In all three patients, tumour was ≤ 5 mm in diameter. Resection margins were clear in all of the patients. None of these patients had breach of the serosa or had any lympho-vascular invasion.

Conclusion: If Meckel's Diverticulum is found incidentally and is morphologically normal then, diverticulectomy is usually enough. If tumour is suspected the question is whether small bowel resection and local lymph node clearance is required? The surgeon might proceed if the tumour had breached the serosa or was >2cm. Additionally, if on histological review tumour was seen at the resection margin or had high grade features then it would be reasonable to consider completion small bowel and mesenteric resection. We highlight the need for a formal consensus regarding the optimal management of Meckel's diverticulum and associated neuroendocrine tumour as well as other tumours.

P017 Use of Molecular imaging to differentiate liver metastases originating from two different primary neoplasms in the same patient.

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Introduction- Synchronous malignant neoplasms in a single patient are well documented in literature. At least 10% of patients with neuroendocrine tumour may develop another cancer, not infrequently colonic adenocarcinoma. FDG PET is recognised as 'standard' imaging for staging metastatic disease in colorectal cancer and recently Gallium-68 DOTA Octreotate PET has been developed as molecular imaging for neuroendocrine tumour staging.

Aims and Methods- To assess molecular imaging utilising (18F) FDG PET scan and Gallium 68 DOTATATE PET scan for differentiating liver metastases arising from colorectal cancer or neuroendocrine tumour in an individual patient. We studied a patient, who had recently undergone left hemicolectomy (Duke's B adenocarcinoma) of the sigmoid colon, was found to have multiple liver metastases and a pancreatic tail mass compatible with neuroendocrine tumour. The patient underwent (18F) FDG PET scan and (68Ga) DOTATATE PET scan. He also underwent ultrasound guided liver biopsies.

Results- The two types of PET scan showed differential uptake in the liver. Some metastases had avid uptake only on the FDG PET and the others only on the Gallium 68 PET, the latter also identifying the pancreatic NET primary. Ultrasound guided liver biopsy specimen confirmed the two types of metastases: moderately differentiated colonic adenocarcinoma and well differentiated neuroendocrine tumour with low grade proliferation index Ki67<2%.

Conclusion- Uptake of specific peptides by tumours is dependant on the biology of the tumour. (18F) FDG PET is very sensitive in detecting metastasis arising from colon cancer in keeping with the fact that FDG PET targets the glucose transporter in these actively multiplying cells. However, neuroendocrine tumours are more indolent, and studies have shown that sensitivity of FDG PET in detecting metastasis in these tumours is much lower. NETs express Somatostatin receptors predominantly subtype-2 which has led to the development of new radio peptides such as (68) Gallium DOTATATE PET, which is much more sensitive and specific in defining distant metastasis related to NETs. We therefore demonstrate the utility of different PET agents for identifying different cancers in an individual patient.

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P018 Case report: An extreme rise in Chromogranin A without a NET

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It is now generally accepted that treatment with proton pump inhibitors (ppi) may cause moderate rises in chromogranin A and gastrin. This has caused difficulties in the diagnosis of gastrinomas which are defined as tumours producing excess gastrin and chromogranin A (CgA). Here we report a patient with extremely high CgA at first investigation:

A 58 year old female with a history of heart failure and type 2 diabetes attended for investigation of upper and lower GI symptoms. Her medication at this initial assessment included spironolactone, eplerenone, and omeprazole. Her plasma CgA was 1250U/l (ref. range 0-30) and gastrin was 75ng/l (ref. range 0-100). Spironolactone was stopped and omeprazole (ppi) was withdrawn for 18 days after which the 2nd sample was taken. The CgA concentration fell dramatically to 22 U/l and gastrin was <30 ng/l. An OGD was performed which showed duodenitis but no peptic ulcer. As the patient complained of severe nausea after ppi withdrawal, this treatment was recommenced. A 3rd sample, taken after a further 10 weeks, showed a raised CgA concentration of 970 U/l and a raised gastrin concentration of 175ng/l. Parietal cell antibodies were absent.

This patient had heart failure and this may cause a modest to moderate increase in CgA. Although it has been suggested (and contended) that spironolactone is associated with increased upper GI bleeding it is unlikely to be the cause of CgA rise. In this case, when spironolactone and ppi were withdrawn, the CgA fell to normal concentrations. When ppi only was reintroduced the CgA rose radically again. It seems that ppi treatment alone is responsible for the extremely high concentrations of CgA and gastrin in this patient.

Although CgA remains the best general marker for neuroendocrine tumours, cases such as this show that its specificity is not absolute. Circulating concentrations of CgA usually associated with neuroendocrine tumours may be observed in patients on ppi therapy. It is therefore necessary to measure both gastrin and CgA and when these are elevated, to withdraw ppi therapy if clinically possible and repeat measurements.

P019 VHL Syndrome – A Case Report

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In 1976, aged twenty, Mr. AJ was diagnosed with a cerebral haemangioblastoma, which was successfully removed. It was noted that his father had died from renal cell carcinoma and a Pheochromocytoma, raising the possibility of VHL Syndrome. Genetic screening was positive but no follow-up was provided and he received no surveillance screening.

In 2004, aged 48, he presented to the gastroenterologists with a two year history of persistent diarrhoea. A CT scan revealed a left sided 1.7cm adrenal mass consistent with an adenoma. Serial 24hr urine metadrenaline ranged between 0.37 – 0.67mmol/l (0-2mmol/l), normetadrenaline ranged between 0.9 -2.06mmol/l(0-5 mmol/l). and 5HIAA analyses ranged between 23-25mmol/d (0-50mmol/d). Fasting Gut hormone profiles were also repeatedly normal (VIP, Pancreatic polypeptide, Glucagon, Somatostatin, gastrin, chromogranin A and B).

A decision was made to manage the lesion conservatively with close radiological and biochemical screening. Over a three year period, the adrenal mass remained unchanged in size and biochemically inactive.

In 2006, surveillance imaging revealed the presence of two spinal haemangioblastoma at the levels of C4 and L1, which were successfully excised.

Earlier this year, the CT scan demonstrated the appearance of two contrast enhancing pancreatic cysts, the largest measuring 1.8x 0.9cm in the head of pancreas. A 1.5cm simple renal cyst, with no sinister radiological features was also noted. Fasting Gut peptides were again normal as was urine cytology. The adrenal lesion was unchanged in size and remained biochemically inactive as assessed by urinary and plasma metanephrines.

A MIBG scan was performed demonstrating increased uptake in the area of the L adrenal gland. Although biochemical screening had not suggested the presence of excess catecholamine secretion, Mr AJ had on occasions experienced symptoms that could be consistent with a phaeochromocytoma. In view of this and the increased uptake on the MIBG scan in the region of the adrenal a decision was made to alpha and beta block pre-operatively, and he received phenoxybenzamine 10mg tds and propranolol 10 mg tds

He underwent a Whipples procedure and L adrenalectomy . Interestingly, the histology of the adrenal gland was consistent with a phaeochromocytoma and the pancreatic lesion suggest a Neuroendocrine Tumour.

P020 Atypical Location and Treatment for a Rare Neuroendocrine Tumor.

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Somatostatinomas are rare neuroendocrine tumors of D cell origin usually arising from the pancreas and duodenum. The symptoms are due to increased somatostatin and include hyperglycemia, cholelithiasis, diarrhea and steatorrhea. Treatment with somatostatin analogue may appear paradoxical, but results in reduced somatostatin levels and symptomatic improvement

Case: A 60yr old gentleman presented with diarrhoea and steatorrhea, opening his bowels between 12-13 times a day causing him to stop working and become depressed. Repeated fasting gut hormone profiles showed an isolated elevated somatostatin level. CT abdomen did not show any pancreatic lesions and colonoscopy was normal. Octreotide scan revealed a well defined lesion in the base of the right lung, confirmed on a CT thorax. Visceral angiography with calcium stimulation and sampling from the femoral artery revealed elevated somatostatin in all samples (> 400pmol/l). Somatostatin levels taken from the right atrium and femoral artery, showed a higher level in the arteries (venous 152pmol/l, arterial 185pmol), suggesting a pulmonary source. However, the surgical risks of resection were thought to be too high. He had a trial of Octreotide therapy without benefit. Therefore he was treated with a combination of Lanreotide 30mg every 14days, and Octreotide 50mcg TDS, resulting in a dramatic improvement in symptoms. He now opens his bowels once or twice a day. His symptoms worsened when Octreotide was withdrawn. He also noticed two days prior to the lanreotide injection he opens his bowels more frequently.

Discussion: There are five subtypes of somatostatin receptors (SSTR). All five SSTRs bind to the natural somatostatin. Two different somatostatin analogues are used clinically, octreotide and lanreotide. These analogues bind principally to the receptor subtype 2 and 5. Although most studies have shown no major difference between octreotide and lanreotide in terms of receptor affinity or biological activity, this case illustrates that combination therapy may have clinical benefits.

P021 Early experience of the Derriford Hospital Neuroendocrine Multi-disciplinary team.

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From the Departments of Cancer Services¹, Endocrinology², Radiology³, Oncology⁴, Gastroenterology⁵, Nuclear Medicine⁶, Urology⁸, and Surgery⁹, Derriford Hospital, Derriford, Plymouth PL6 8DH and Oncology⁷, Torbay Hospital, Torquay, Devon TQ2 7AA.

Aim

To describe the initial experience of the Plymouth Neuroendocrine Multidisciplinary Team.

Background

Prior to Dec 2006 patients with neuroendocrine disease were identified and treatment planned at number of MDT meetings of different tumour sites including, upper and lower GI cancer, urology and endocrinology. Subsequent treatment was often undertaken in major centres outside the Southwest Peninsula. In view of the development of specialised services in Derriford Hospital including therapeutic nuclear medicine, minimally invasive adrenal surgery and hepatobiliary surgery a specialised neuroendocrine MDT was established in December 2006 to provide a focus for shared care of these varied tumours. This MDT meets once per month and has representation from radiology, oncology, surgery, gastroenterology and endocrinology.

Methods

Agendae of all meetings since the inception of the MDT in December 2006 were retrieved from the MDT coordinators records and data were extracted to create a database.

Results

The MDT has met on 21 occasions to date and 120 case discussions have been held on 72 patients. Ninety-four of the case discussions involved patients from Derriford Hospital, Plymouth. All hospitals in the Peninsula have referred patients for discussion and treatment with the largest number of regional referrals coming from Truro (15 case discussions).

Adrenal neuroendocrine tumours form the largest group of patients under discussion (44) with carcinoid tumours (25) and pancreatic endocrine tumours (15) forming the other large tumour groups.

Conclusion

Adrenal tumours form the largest patient group under discussion reflecting the established nature of the regional service for phaeochromocytoma. The number of cases from other tumour sites is growing and local expertise in the management of these problems is increasing. Plans are underway to establish a 'virtual' MDT using teleconferencing with an audiovisual link to create the first network-wide MDT in the Southwest Peninsula.

P022 Case Report: Prophylactic Thyroidectomy For Increasing Calcitonin Levels?

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A 19yr old man was referred to Endocrinology Clinic with a minimally raised calcitonin level. He had a past history of primary hyperparathyroidism resulting in renal colic aged 17yrs, and underwent three gland parathyroidectomy aged 18yrs. Histology demonstrated a single right lower parathyroid adenoma with normal thyroid biopsy. He has no family history of endocrine disease and is a non-smoker. His calcium has remained normal since with detectable PTH. Over 5 years there has been a progressive increase in his basal calcitonin level:

Date	Feb '04	Sep '05	Jul-Oct '06	Dec '06	Feb '07	Jul '08
Calcitonin (ng/L)	14.1	15.8	34.1-32.9	41.3	49.1	46.8
Normal range (ng/L)	11.5*	11.5	18.9	18.9	18.9	18.9**

Peak calcitonin during a pentagastrin stimulation test was 152.0 in 2004* and 173.0 in July 2008.** His CEA, urinary catecholamines and fasting gut hormones have remained normal. Genetic screening for MEN-1 and MEN-2 (*RET* exons 1-20) was negative. Yearly thyroid ultrasound scans have been normal. An MRI neck scan was normal in 2004, and a Dimercaptosuccinic Acid (DMSA) scan was normal in 2006. He is now 24yrs old. Despite the development of primary hyperparathyroidism at a young age and an increasingly elevated calcitonin level, there has been no histological evidence of C-cell hyperplasia, genetic evidence for increased risk of medullary thyroid carcinoma (MTC), nor radiological evidence of MTC. There are surgical risks of hypoparathyroidism and voice change with repeat neck surgery. Our Multidisciplinary Endocrine Meeting has concluded that there is no current indication for prophylactic thyroidectomy. The follow-up plan is for annual assay of calcitonin and neck ultrasound scans with fine needle aspiration of any thyroid nodules. In the absence of a suspicious nodule, it is open for discussion whether there is a level of basal or stimulated calcitonin which should prompt further consideration of prophylactic thyroidectomy.

P023 Metastatic poorly differentiated neuroendocrine carcinoma (PDNC) of unknown primary – Unusual clinical presentations.

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Introduction: Cancer of unknown primary accounts for 2% of all cancer diagnoses and less than 5% of these histologic subgroups have neuroendocrine differentiation. Although neuroendocrine metastases to the liver from undetected primary sites are well recognised we present three very unusual clinical presentations of this subgroup.

Case 1: 34 year old lady presenting with a left posterior fossa midline tumour underwent a posterior fossa craniotomy with resection, which confirmed a TTF1 positive metastatic PDNC. Staging CT revealed 4.2 cm nodal mass adjacent to left external iliac vessel and an octreotide scan was negative. Primary site did not become evident for a further 6 months.

Case 2: 79 year old gentleman presented with 2 week history of intermittent rectal bleeding due to a 4cm rectosigmoid polyp (adenocarcinoma), with no disseminated disease detected on staging CT scan. Hartman's procedure revealed moderately differentiated rectal adenocarcinoma but 17/33 mesorectal lymph nodes and the extramural vascular components of the tumour contained a moderately - PDNC which was negative for TTF1. Octreotide scan and fasting gut hormone profile were normal and CT scan did not reveal any obvious second primary.

Case 3: 88 year old gentleman with 9 week history of scrotal and right leg oedema had extensive lytic bony metastases, widespread retroperitoneal lymphadenopathy causing caval compromise and enlarged prostate. Histology from lytic lesion in sternum confirmed PDNC with TTF1 positivity. Further investigations did not reveal a definite primary site although prostatic enlargement was observed on CT.

Discussion: Through further discussion of the investigations and management of our cases in the context of the known literature we will attempt to highlight some of the difficulties involved in the clinical care of patients with this rare presentation.

P024 Unusual presentation of a Neuro Endocrine Tumour with endometrial and ovarian metastasis.

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The clinical course of metastatic Neuro Endocrine Tumour (NET) can be variable. We present a case of Carcinoid presenting with metastatic disease in ovaries and endometrium with an unusual presentation of vaginal bleeding.

A 63 year old lady with 6 month history of upper abdomen pain was diagnosed with biliary calculi. Diagnostic laparoscopy showed peritoneal malignancy with unknown primary. Peritoneal biopsy revealed a metastatic NET with cells strongly positive for NSE and Chromogranin A with focal positivity for CD56. Ki 67 staining showed low proliferation index. Urinary 5HIAA was slightly elevated. Octreoscan showed an area of positivity in the right iliac fossa. CT scan confirmed thickening of the terminal ileum with a possible node corresponding to the area of uptake in the Octreoscan. She was initially treated with Octreotide which improved her symptoms. Few months later she underwent laparoscopic cholecystectomy followed by right hemi-colectomy. Biopsy confirmed well differentiated neuro endocrine tumour of the terminal ileum. Though the tumour was completely excised it was found to be extending into the serosal surface. She was continued with Somatostatin analogue.

A year later she presented to a different hospital with vaginal bleeding. As the endometrial biopsy suggested endometrial adenocarcinoma, total abdominal hysterectomy with bilateral salpingo-oophorectomy was planned. With timely consultation with endocrinologists who treated her NET initially, the surgery was performed under Octreotide infusion cover. Histopathology showed features of grade 2 endometrial adenocarcinoma which stained positively for CK7, CA125, CD99 and focal staining for Chromogranin, and NSE. The ovarian tumour was strongly positive for neuroendocrine markers like chromogranin, Synaptophysin and NSE. The multiplicity and the surface location in the ovaries would suggest this to be metastatic in nature.

This case highlights the widely variable presentation of NET and the need to have high index of suspicion of metastatic disease in a person with known NET. Surgery without Octreotide cover will lead to adverse consequences in such cases.

P025 Mesenteric fibrosis in patients with small bowel carcinoid tumours: impact on quality of life and survival.

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Background

Small bowel carcinoid tumours are generally indolent, slowly progressive malignancies. Development of mesenteric fibrosis is a well documented feature in these tumours; it is probably associated to biogenic amine secretion and can result in development of a plethora of complications 1.

Aim

To perform a retrospective analysis of 62 patients with small bowel carcinoids, who all had radiological evidence of mesenteric fibrosis to identify systemic complications, management and impact on morbidity and mortality.

Methods

Sixty two out of 216 patients with small bowel carcinoid tumours had radiological evidence of mesenteric fibrosis and were included in the study. All patients had a histological diagnosis of carcinoid tumour. The tumours were classified (according to WHO) into low-grade, intermediate grade, and high-grade neuroendocrine tumours. The cohort was divided into two groups dependent on the presence of signs or symptoms related to mesenteric fibrosis; these comprised of small bowel obstruction and/or post prandial abdominal pain. The groups were compared for surgical intervention, presence of carcinoid heart disease and survival. Statistical analysis was performed using SPSS.

Results

Forty five patients had clinical features related to mesenteric fibrosis, whilst the remaining 17 patients were asymptomatic Pearson Chi Square test comparing symptomatic group vs asymptomatic showed no difference in terms of histological grade of tumour, sex and carcinoid heart disease. Average duration of follow-up for all patients 59.7 months.

Surgical intervention had been performed in 30 of the 45 symptomatic patients. The indication for surgery was related to small bowel obstruction in 26 cases, and related to hydronephrosis in 4 cases. Seven of 17 patients (41.4%) in the asymptomatic group have died, whilst 24 of 45 patients (53.3%) in the symptomatic group died. The overall survival for both asymptomatic and symptomatic patients was the same. However, Kaplan Meier analysis showed improved survival for patients that underwent surgery for complication related to mesenteric fibrosis than those that had no surgical intervention at any point of their treatment ($p < 0.001$). Kaplan Meier analysis showed that tumour grade was also a prognostic marker, with low grade tumour having a significantly better outcome than intermediate or high grade tumours ($p < 0.001$).

Conclusion

In symptomatic patients complications from mesenteric fibrosis are a major cause of mortality and morbidity. The primary cause of death is related to complication from mesenteric fibrosis rather than progression of disease. In asymptomatic patients with midgut tumours the cause of death is often related to tumour load. This study had shown surgical intervention for bowel obstruction showed improved outcome when compared to those without surgical intervention. This data implies that surgical intervention when possible in patients with small bowel obstruction due to mesenteric fibrosis can improve survival.

P026 A Pheochromocytoma disguised as an Acute Coronary Syndrome

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Pheochromocytoma can mimic many other conditions making the diagnosis difficult, but often the most important aspect is to firstly consider a pheochromocytoma in the differential diagnosis. A 39 year old Asian man developed acute onset chest pain whilst using the treadmill at the gym. This was associated with palpitations, nausea, vomiting and flushing. This initial episode lasted 5 minutes but recurred 3 times post-exercise. He attended A&E where an ECG showed global T wave inversion. Troponin was elevated at 2.9ug/L (0-0.032). He was an ex-smoker with no family history of IHD and had a normal lipid profile.

Of note he had had a similar presentation 3 years previously, also after exercise, and underwent coronary angiography that was normal.

He was initially treated as an acute coronary syndrome with aspirin, clopidogrel and enoxaparin. His condition deteriorated over the next few hours and he developed pulmonary oedema. Echocardiogram showed regional wall abnormalities and impaired LV function. He had a labile blood pressure, tachycardia and mild renal impairment.

Renal USS was performed to look for renal artery stenosis, but a large left adrenal mass was identified, raising the suspicion of a pheochromocytoma. Based on this clinical diagnosis he was commenced on alpha adrenoreceptor blockade with intravenous phenoxybenzamine. Within hours his blood pressure normalised and his pulmonary oedema resolved. He had no further chest pain. He was converted to oral phenoxybenzamine therapy and beta blocker was added. Subsequent imaging with a CT abdomen confirmed a 7cm x 7cm adrenal mass with central necrosis. MIBG scan showed medium grade tracer uptake at 4 hours with a photopenic necrotic centre, and high grade tracer uptake at 24 hours, in keeping with the appearances of a pheochromocytoma. The patient underwent an elective laparoscopic adrenalectomy under full alpha and beta blockade, and histology confirmed a pheochromocytoma.

In conclusion, the acute presentation was of a catecholamine-induced myocarditis, secondary to a pheochromocytoma. The initial clinical history appeared typical for acute coronary syndrome and yet he had no risk factors for ACS. In addition a previous normal angiogram highlighted the need to look for an alternative diagnosis.

P027 Cardiac complications of neuroendocrine tumours

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We present 3 cases from the Edinburgh Cancer Centre on cardiac complications of neuroendocrine tumours.

Case 1: A 71 year old gentleman initially presented with a one year history of flushing, weight loss, chronic diarrhoea and hepatic metastases; biopsy confirmed a neuroendocrine tumour. 6 months later, he was admitted with worsening dyspnoea and cyanosis (O₂ saturations 88% on 85% oxygen). Pulmonary embolism was excluded. An echocardiogram revealed a fixed open tricuspid valve with normal pulmonary artery pressure while a bubble contrast study revealed a right to left shunt which was confirmed to be due to flow across a patent foramen ovale on a trans-oesophageal echocardiogram. The cardiac defect was closed with a 25 mm Amplatzer occluder with his O₂ saturations on air immediately increasing from 82 to 95%.

Case 2: A 54 year old lady with an 18 month history of carcinoid tumour and liver metastases was admitted as an emergency with a 2 week history of increasing shortness of breath. Examination revealed peripheral oedema, bibasal crepitations and a 3/6 pan systolic murmur at the apex radiating to the axilla. Cardiac investigation showed severe mitral regurgitation, significant aortic regurgitation, normal coronary arteries and LV ejection fraction of 45%. She underwent double valve replacement and pathology revealed mildly thickened valves with oedematous myxoid change within the stroma suggestive of a degenerative process. She remained immobile due to gross peripheral oedema and died of respiratory sepsis one month post operatively

Case 3: A 73 year old gentleman initially presented with hot flushes for 2 years then palpitations and features of right heart failure over the preceding two months. He had extensive liver metastases and a mesenteric mass. Biopsy confirmed a metastatic neuroendocrine tumour while echocardiogram revealed severe tricuspid regurgitation. He required atenolol for cardiac arrhythmias and diuretics for peripheral oedema. He lost 8 kg, developed ascites and mild renal failure due to ureteric obstruction from his mesenteric mass prior to his death 17 months later. A post-mortem examination confirmed the previous findings but also revealed a small intestinal primary and an enlarged right ventricle.

P028 Unusual Case of Hyperpigmentation

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Cutaneous pigmentation results from the synthesis of melanin by the melanocytes. Its distribution pattern in the surrounding keratinocytes determines the actual colour of the skin. ACTH and α MSH are equipotent at the melanocortin-1 receptor (MC-1R) that is expressed on the cell surface of melanocytes. Activation of these receptors stimulates both proliferation of melanocytes and melanin synthesis.

We present the case of a 66-year-old lady. Originally from Ghana, she has lived in the UK for over 40yrs. She presented with an 18 month history of generalised hyperpigmentation. Cortisol day curve and a random ACTH were both normal. A skin biopsy showed a normal number of melanocytes but with hyperpigmentation of the dermis and epidermis. Levels of Alpha-MSH levels were undetectable in the plasma. MRI pituitary was normal. Imaging revealed an octreotide avid lesion within the mid zone of the left lung. Unfortunately CT thorax following the octreotide scan did not show any corresponding lesion.

Her skin continued to darken. She went back to Ghana for a holiday where unfortunately she was shunned by her family, as there was a belief that she was cursed. She is extremely desperate for a cure however but is not keen on having surgery.

Discussion:

Our alpha-MSH assay is validated for in vitro release from hypothalamic explants. Its accuracy on plasma samples is unknown. An alpha-MSH secreting tumor therefore cannot be excluded. Other options for therapy include octreotide or surgery. However, the success of therapy will be difficult to judge as any improvement in this lady's skin colour is likely to be slow.

P029 MEN1: the full house

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This gentleman was diagnosed with hyperparathyroidism at the age of 34 and was subsequently found to have multiple manifestations of MEN1.

Hyperparathyroidism

He was diagnosed with hyperparathyroidism and underwent a parathyroidectomy in 2002 with removal of 2 glands. Four years later calcium levels were raised once again and two further hyperplastic glands were removed, with cure of his hypercalcaemia. He is maintained with alfacalcidol, although his PTH is still detectable.

Gastrinoma and other pancreatic islet cell tumours

He developed heartburn, nausea, vomiting and abdominal pain, and on upper GI endoscopy was found to have moderate duodenitis. He was started on lansoprazole with immediate relief of his symptoms. Blood tests showed elevated gastrin, chromogranins A and B, glucagon and pancreatic polypeptide suggestive of a gastrinoma and other islet cell tumours. Imaging, including a CT abdomen, a PET scan and visceral angiography revealed multiple duodenal and pancreatic lesions. Calcium stimulation tests revealed no discrete gastrin releasing foci amenable to surgery.

Pituitary disease: Cushing's disease and prolactinoma

He complained of impotence, reduced libido, weight gain and appeared Cushingoid. Two small anterior pituitary lesions were seen on pituitary MRI. Cushing's disease and a prolactinoma were diagnosed on the basis of elevated urinary cortisols, failure to suppress cortisol during a low dose dexamethasone suppression test, inferior petrosal sinus sampling showing a central source of ACTH excess and elevated prolactin, around 1700 mU/L. The patient underwent trans-sphenoidal hypophysectomy. He was started on hydrocortisone, DDAVP, thyroxine and testosterone replacement. A recent MRI of the pituitary showed a normal residual gland.

Adrenal lesions

A CT scan of the adrenals showed bilateral nodular adrenal enlargement. Pheochromocytoma was excluded on the basis of normal catecholamine excretions.

Other lesions: lipomata

He developed lipomas on his zygomatic arch and thigh and an angiofibroma on the nose.

Genetic testing

MEN1 was confirmed on genetic testing. One of his 3 siblings aged 14 was found to have an MEN1 mutation.

Conclusions

Our patient developed a full house of endocrine neoplasias related to his MEN1. He presented a diagnostic and management challenge requiring a multi-disciplinary approach to address the nature of the disease.

P030 Primary adrenocortical insufficiency despite a “normal” short synacthen test

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A 60 year old gentleman who had previously undergone a right nephrectomy for renal cell carcinoma was admitted electively for a left adrenalectomy due to metastatic disease. Prior to this he had been treated with immunotherapy (Sunitinib) and radiotherapy for pulmonary and bony metastases respectively. He was given perioperative cover with hydrocortisone. A short synacthen test (SST) performed the morning after discontinuing hydrocortisone showed a baseline cortisol of 406nmol/L rising to 469nmol/L at 30 minutes and 555nmol/L at 60 minutes. He was clinically euadrenal, so it was decided that he did not require further hydrocortisone. He was discharged home 3 days later. Three weeks later he presented with profound nausea and tiredness. On examination he had postural hypotension. Plasma sodium was 129mmol/L, potassium 4.4mmol/L and random cortisol 689nmol/L. He was started on hydrocortisone 20mg, 10mg, 10mg and fludrocortisone 100mcg once daily. His symptoms resolved over the next 48 hours, and the hydrocortisone was reduced to 10mg, 5mg, 5mg prior to review in endocrinology out-patients. At out-patient review, it was noted that the baseline ACTH from his earlier SST was elevated at 52.0ng/L suggesting subclinical hypocortisolaemia. The dose of his hydrocortisone was increased to 15mg, 10mg, 5mg, as he is about to start further immunotherapy (Bevacizumab). We present a case of what we believe to be adrenal toxicity due to Sunitinib, with clinical findings and investigations suggesting predominantly mineralocorticoid deficiency. Adrenal toxicity with Sunitinib has been reported previously in animals but not humans. Such subclinical toxicity may be difficult to detect unless unmasked by physiological stressors. We highlight the importance of knowing both a baseline ACTH and peak cortisol when interpreting a SST, and also the difficulty in determining what is an appropriate random cortisol in an acutely unwell patient. Another potential explanation for the discordance between cortisol results and his clinical state is abnormal cortisol binding globulin levels, which must be considered.

P031 Adrenocortical carcinoma presenting as Cushing's syndrome: 2 case reports

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A sixty-nine year old lady presented with pancreatitis, which was managed conservatively and resolved. However, imaging identified a 4cm left adrenal lesion. She had no features of Cushing's syndrome, and was normotensive, but serum potassium was low. Renin:aldosterone ratio was normal. She failed a low dose dexamethasone suppression test (LDDST). She underwent laparoscopic adrenalectomy. Histology showed an adrenocortical carcinoma extending into the adjacent adipose tissue. Sixteen months postoperatively she failed an LDDST. A MRI adrenals showed a 1.5x1.4 cm soft tissue mass, thought to represent recurrence of the adrenocortical carcinoma. She underwent repeat surgery with removal of the recurrent tumour, the left kidney, the spleen and a segment of colon. The histology showed multifocal adrenocortical carcinoma involving the previous surgical bed. She was commenced on a course of mitotane. Twenty-two months after her initial surgery, imaging was performed in view of abdominal pain. This showed local recurrence and peritoneal deposits. A sixty-year old man was referred to our centre with a diagnosis of ACTH independent Cushing's syndrome and a 7.6cm right adrenal mass, after presenting with hypertension. A CT with contrast suggested that this was a benign lesion. He underwent an open adrenalectomy, as the lesion was closely applied to the liver. Histology identified an adrenocortical tumour with a high mitotic rate and a Ki67 index >5%. This was consistent with an adrenocortical carcinoma, and there was evidence of involvement of peri-adrenal fat. He subsequently underwent chemotherapy with mitotane. Mitotane is a synthetic derivative of the insecticide DDT. It inhibits cortisone metabolism, and also has cytotoxic effects on the adrenal cortex. Its role in the management of adrenocortical carcinoma is unclear. Recent retrospective data suggest that it should be used as adjuvant treatment following surgery, and should not be solely reserved for recurrent disease. The rarity of adrenocortical carcinoma makes the undertaking of adequately powered randomised trials difficult.