

An update on the evolving epidemiology, biology and prognosis of neuroendocrine neoplasms

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Although much has been learned about the biology and natural history of neuroendocrine neoplasms over the past two decades, our understanding of these topics is still evolving due to continuing improvements in molecular diagnostics and therapeutics. Our recent analyses using Surveillance, Epidemiology, and End Results (SEER) registry data showed the incidence and prevalence of neuroendocrine tumors are continuing to rise (Dasari et al, JAMA Oncology 2017). The age-adjusted incidence rate increased 6.4-fold from 1973 (1.09 per 100 000) to 2012 (6.98 per 100 000). The estimated 20-year limited-duration prevalence of NETs in the United States on January 1, 2014, was 171,321. The overall survival for all NETs improved from the 2000-2004 period to the 2009-2012 period (hazard ratio [HR], 0.79; 95%CI, 0.73-0.85). Even larger increases in OS between these periods were noted in distant-stage gastrointestinal NETs (HR, 0.71; 95%CI, 0.62-0.81) and distant-stage pancreatic NETs (HR, 0.56; 95%CI, 0.44-0.70). Using SEER data linked to Medicare claims database, we showed that carcinoid syndrome is significantly associated with tumor grade, stage, and primary tumor site, and leads to shorter survival compared with those patients without carcinoid syndrome (Halperin et al, Lancet Oncol 2017). We also leveraged data from these sources to examine the recurrence rates after surgery and demonstrated likelihood of recurrence varied by grade, stage, primary tumor size and primary site (Shen et al, Annals of Oncology 2017). Our study suggests that surveillance recommendations should be tailored according to patient and tumor characteristics after resection. Surveillance past 5 years may be avoided in elderly patients with competing morbidities or low risk of recurrence.

Endocrine features of NETs

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The natural history of patients with neuroendocrine neoplasms (NENs) is characterized by pronounced interpatient heterogeneity. This clinical variability reflects the diverse biology of NENs that show a wide spectrum of cell differentiation, proliferation, and invasiveness. A major determinant of the clinical course is attributed to the increased production and secretion of a multitude of neuropeptides and amines that cause distinct clinical syndromes. Over-secretion of a single hormone (functioning tumor) or absence of any hormonal over-secretion (non-functioning tumor) are the two most common clinical scenarios observed in NENs patients with sporadic disease. However, concomitant secretion of multiple peptides at diagnosis can be observed in patients with multiple endocrine neoplasia syndromes and is attributed to the coexistence of tumors of separate origins. The concurrent secretion of multiple hormones at diagnosis as well as the development of secondary hormone secretion have been described to occur in a minority (9.3%) of sporadic NENs patients, mainly of pancreatic origin, in the presence of metastatic disease. Secondary hormone secretion was associated with disease progression as well as with increased morbidity and mortality. Patients with metastatic NENs should be closely monitored for the appearance of clinical symptoms of secondary hormone secretion during the disease course; a timely diagnosis requiring a high index of suspicion is major in order to improve the outcomes of these patients. The molecular basis underlying production and secretion of different hormones in NENs is poorly studied, though hormonal plasticity and reprogramming of the hormone secretion have been shown to occur both spontaneously or during experimental manipulation.

Familial syndromes - when to suspect and how to investigate

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An overview of the clinical features of the inherited Neuroendocrine syndromes and when they should be suspected.

Clinical, Genetic, and Molecular Characterizations of Pheochromocytoma in MEN2

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Introduction: Pheochromocytomas and paragangliomas are neuroendocrine tumors of the adrenal medulla and extra-adrenal paraganglia, respectively. MEN2 is an autosomal dominant genetic condition caused by a mutation in the *RET* proto-oncogene

Aim: To characterize the clinical features of MEN2 patients, and to evaluate genotype-phenotype correlation

Methods: We conducted a retrospective analysis of prospectively collected data after screening the protocol for patients with MEN2 and identified 43 patients to include in this study. Statistical analyses performed using descriptive statistics and Chi-Square test for association

Results: The study group consisted of 43 patients with MEN2 associated PHEO, 27 of which were confirmed through genetic testing to have the mutation in the *RET* proto-oncogene. 51.85% (14/27) of patients with germline *RET*+ MEN2 mutations

showed the change in exon 11. In exon 11, the most frequent DNA changes at 18.52% each (5/27) were in c.1900 from T>C and c.1901 from G>A. No genotype-phenotype association was detected. Average age at diagnosis is 35, bilateral pheochromocytoma was found in 38.9% (14/36), extraadrenal Pheochromocytoma in 30.8%. 18F-DOPA PET/CT had Sensitivity: 90.91%, specificity: 33.33%, PVV: 83.33%, NPV: 50%, while 131I-mIBG scans have Sensitivity: 83.33%, specificity: 100%, PPV: 100%, NPV: 40%. Noradrenergic profile found in 13.51% (5/37) of patients; and adrenergic in 23.33% (7/30) of patients, while mixed biochemical profile was found in only 6% of patients (2/30). 40% (16/40) of patients were reported to have MTC, of which 68.75% (11/16) had metastatic MTC. Using Chi-Square test, DNA sequence was not associated with early diagnosis with $X^2 = 10.9$, corresponding with $P\text{-Value} = 0.36$. or bilateral adrenal disease with $X^2 = 17.7$, corresponding with $P\text{-Value} = 0.08$. or extra-adrenal disease with $X^2 = 16.9$ with $P\text{-Value} = 0.15$

Conclusion: In this study, we present descriptive characterizations of Pheochromocytoma in MEN2. F-Dopa found to be an excellent functional imaging modality for diagnosing Pheo in MEN2. No genotype-phenotype correlation was found

1. Thosani S, Ayala-Ramirez M, Palmer L, Hu MI, Rich T, Gagel RF, Cote G, Waguespack SG, Habra MA, Jimenez C. The characterization of pheochromocytoma and its impact on overall survival in multiple endocrine neoplasia type 2. *J Clin Endocrinol Metab.* 2013;98(11):E1813–E1819.
2. Pacak K, Eisenhofer G, Ilias I. Diagnosis of pheochromocytoma with special emphasis on MEN2 syndrome. *Hormones (Athens)* 2009;8(2):111–116.

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Pathological classification

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Radiological Imaging of NETs

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The role of radiological imaging, the strength and limitations of radiology modalities as well as their key imaging features will be discussed and presented.

Radiological imaging has a role in the detection of primary NET, defining its local extent and anatomical relationship to adjacent structures, metastatic staging especially when surgical resection is being considered, monitoring for complication and response as well as assessment of recurrent disease.

The key radiology imaging modalities are Computed Tomography CT and Magnetic Resonance Imaging MRI, with ultrasound playing a supplementary role, often as the imaging tool to guide tissue biopsy of liver or nodal metastatic disease.

Contrast enhanced multi detector CT of the chest, abdomen and pelvis, including triple phase images of the liver, represents the primary imaging method for NET in various stages of its disease course. CT is widely available and image acquisition is fast, providing high resolution images in multiple planes. CT is limited in its ability to assess nodal and bony disease. The advent of dual energy CT provides the opportunity to obtain virtual precontrast images and has the potential to improve tumour-background contrast and sensitivity.

Contrast enhanced MRI provides better soft tissue contrast and is the radiology modality of choice in assessing the extent of liver metastatic disease, especially when hepatocyte-specific contrast agent and diffusion weighted imaging are used. MR cholangio-pancreatography can also be performed to assess the biliary and pancreatic ducts.

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Molecular imaging in diagnosis and treatment planning

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Molecular imaging is changing diagnostic and treatment paradigms in patients with neuroendocrine tumors through its ability to non-invasively characterize disease, supplementing the traditional role of using imaging for localizing and measuring disease. For patients with metastatic disease, there is an increasing range of therapies but these must be individualized to the specific subtype of tumor expressed, which varies in aggressiveness from well to poorly differentiated phenotypes. Positron emission tomography (PET) is now able to characterize these subtypes through its ability to quantify somatostatin receptor cell surface (SSTR) expression and glycolytic metabolism with SSTR and fluorodeoxyglucose (FDG) PET, respectively. The ability to perform this as a whole body study is highlighting the limitations of relying on histopathology obtained from a single site. Through earlier diagnosis, improved selection of the most appropriate therapy and better assessment of therapeutic response for an individual patient, molecular imaging is improving the outcome for patients with NET.

The prognostic impact of dual FDG/somatostatin receptor PET in metastatic neuroendocrine tumours: updated overall survival from the NETPET study

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Aims: [F-18]-FDG and [Ga-68]-DOTATATE PET scans are increasingly used in NETs. FDG avidity is associated with high-grade disease and poor prognosis, and DOTATATE avidity is associated with low-grade disease and improved prognosis. However, there is no consensus regarding interpretation of dual PET imaging. We have previously presented a novel proposal for scoring dual FDG/DOTATATE PET (the NETPET score) in metastatic NET (Chan Theranostics 2017). Here we present the updated overall survival findings from the retrospective study.

Methods: Retrospective study of patients with metastatic NET who underwent both FDG and DOTATATE PET/CT within 31 days of each other. The NETPET score was developed as follows: P1 – DOTA+FDG- disease only, P2-P4 – both DOTA+ and FDG+ disease, P5 – significant FDG+DOTA- disease. The score was applied to paired scans by two experienced nuclear medicine physicians. We assessed correlation between NETPET score and histological grade. Potential predictors of overall survival (age, grade, extrahepatic disease, NETPET score) were assessed by univariate and multivariate analysis.

Results: 62 patients (median age 60 years, 35% female; 17 Grade 1, 26 Grade 2, 15 Grade 3) were eligible for inclusion. NETPET score was correlated with histological grade (Chi-squared test, $p=0.0001$). At the time of analysis, 35/62 patients were still alive (median follow-up 50 months). Median overall survival was as follows: P1 – not reached, P2-4 – not reached (projected 48 months), P5 – 11 months. On univariate analysis, age ($p=0.014$) and NETPET score ($p=0.0011$) were significantly associated with overall survival but histological grade ($p=0.321$) and extrahepatic disease ($p=0.068$) were not. On multivariate analysis, NETPET score alone ($p<0.001$) was associated with overall survival.

Conclusions: NETPET score is correlated with histological grade and also overall survival (independent of histological grade). Dual FDG/DOTATATE PET is a promising tool for “whole body molecular biopsy” of NET and should be tested prospectively.

1. Chan DL, Pavlakis N, Schembri GP, Bernard EJ, Hsiao E, Hayes A et al. Dual Somatostatin Receptor/FDG PET/CT Imaging in Metastatic Neuroendocrine Tumours: Proposal for a Novel Grading Scheme with Prognostic Significance. *Theranostics* 2017 Mar 1;7(5):1149-1158.

Unicorn foundation

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Survivorship considerations for people with NETs

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Neuroendocrine tumours (NETs) are an uncommon but heterogeneous group of malignancies; incidence and prevalence is rising.

There is little literature that specifically deals with the concerns and issues experienced by people living with and beyond a diagnosis of NET (that is, survivors). Limited extant data suggests that NET survivors experience many issues that are similar to other survivor groups, including physical concerns, such as fatigue and pain; emotional issues, such as fear of cancer spreading, uncertainty about the future, and depression; altered relationships; financial concerns; role and lifestyle changes, and changes in work. They may also experience unique symptom issues, including diarrhoea, cramping and breathlessness. These issues need to be identified and appropriately managed.

Survivors frequently encounter inexperienced health care professionals and poor communication between providers, resulting in suboptimal care. As with other survivor groups, consideration should be given to models of care that may not be medically led or face-to-face. These might include greater use of nurse-led review and better integration with primary care, as well the

use of phone and internet-based reviews, and remote monitoring. Many providers (including primary care practitioners) likely lack the information and guidance necessary to adequately care for survivors.

Preliminary data suggests that NET survivors value survivorship care plans (SCPs). SCPs have been endorsed internationally. They include a summary of diagnosis and treatments, recommended follow up, and strategies to remain well.

More evidence is needed to guide effective follow up care, including regarding the frequency of visits and use of various testing. Existing international guidelines have a relatively narrow focus and should be broadened to consider the whole patient experience.

There are many research gaps, including better describing the short and long-term experiences and unmet needs of survivors, establishing the most effective management of late and long term issues, strengthening the evidence around surveillance, and development of sustainable, cost-effective models of care.

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Nutritional aspects, including short gut syndrome

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The pathophysiology of neuroendocrine tumours and their treatment can cause various symptoms with the potential to impact on nutritional factors such as vitamin synthesis and absorption, dietary habits, weight change and appetite. Patients with serotonin producing NETs and those on somatostatin analogue treatment are at risk of malabsorption syndromes, leading to potential deficiency in fat-soluble vitamins and niacin. Bowel resection leads to additional risk of malabsorption and malnutrition. Malnutrition and dietary modification is prevalent in NET patients, with up to 40-90% of patients reporting food intolerances or changing their diet to manage symptoms. Recent research has indicated that up to 38% of NET patients are at nutritional risk. Diarrhoea, flushing, abdominal pain and bloating are symptoms commonly misdiagnosed in NET patients, and have a significant impact on patients' quality of life. Common nutrition issues reported by NET patients will be discussed, as well as recommendations for suitable screening and management practices.

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Identifying nutritional concerns and dietary support requirements for patients with neuroendocrine tumours

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Introduction: Neuroendocrine Tumours (NETs) are a diverse group of tumours arising from cells of the neuroendocrine system. NETs have a large impact on a patient's quality of life due to symptoms caused through hormonal imbalance, for example diarrhoea, constipation and abdominal pain. Many of these symptoms and treatments provided to NET patients have an impact on nutritional status, yet there is little nutrition information available for NET patients.

Aim: To identify current nutritional issues and nutrition knowledge of NET patients in New Zealand (NZ) to inform a nutritional toolkit which will be created as the secondary phase of this study.

Methods: An online survey was conducted from 26th March to 23rd April 2018. Participants were recruited through the Unicorn Foundation NZ networks.

Results: Fifty seven participants completed the survey (74.6% female). Symptoms were reported by 89.5% (n= 51) of participants, and the most common reported symptoms were fatigue/weakness, diarrhoea, and gas/bloating (n= 39, 36 and 35 respectively). Almost two thirds (74.5%) of participants experienced five or more symptoms, with one participant reporting 17 symptoms in total. Only 12 (21%) participants reported receiving dietary information after their NET diagnosis, however 70.2% (n=40) of participants had made dietary changes after diagnosis.

Discussion: This study demonstrates that NET patients in NZ are experiencing a large range of symptoms which could have an effect on their nutritional status. Many reported they were not receiving adequate, if any, dietary support for management of these symptoms, and therefore were self-managing changes to their diet. It also shows that NET cases are very diverse, hence dietary information provided needs to be tailored to the individual. It is apparent that a nutritional toolkit coupled with individualised dietetic therapy would be highly valuable to this group of patients.

Perceptions of care and patient-reported outcomes in people living with neuroendocrine tumours

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Background: Neuroendocrine tumours (NETs) are rare and when metastatic are incurable but slow growing. Patients may be confronted with disease-specific problems and distinct issues when accessing health-care. We aimed to assess perceptions of care coordination, identify unmet needs and examine if these varied by whether patients received specialist oncology care in a single hospital or shared between that and another hospital. We also quantified anxiety, depression and NET-related physical symptoms.

Methods: We conducted a cross-sectional survey of 111 NET patients managed at Royal Brisbane and Women's Hospital. Validated surveys measured care coordination (CCCQ), unmet needs (SCNS-SF34), anxiety and depression (HADS), and quality of life and symptoms (FACT).

Results: Participants were between 2 months and 27 years after diagnosis. The worst-ranked items on the CCCQ related to health professionals having a full case history, providing information about financial entitlements and asking about how well patients and their families were coping. People with shared care were significantly less satisfied with some aspects of care. One-in-three participants reported a moderate-to-high unmet need for help with fatigue and one-in-four with psychological concerns about their cancer spreading, uncertainty about their future and about the worries of those close to them. Overall, 30% of participants had anxiety and 20% had depression and they had significantly lower physical and emotional wellbeing compared to the general population.

Conclusions: NETs are experienced as a chronic illness. In addition to ongoing psychological and physical symptoms management, improvements to case history documentation and discussions about coping and finance are recommended.

Unmet needs in the global NETs patient community: an assessment of major gaps from the perspectives of patients, patient advocates and NET health professionals

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Aim: The International Neuroendocrine Cancer Alliance (INCA) undertook a survey to assess needs in quality care for NET patients.

Methods: In 2017, patients and family, healthcare professionals (HCPs) and patient advocates completed an online survey about NET information, standards of care, diagnostics/treatment and research.

Results: There were 443 respondents from 26 countries (338 patient/family; 70 HCPs; 35 advocates). Patients reported several information gaps at diagnosis that were not perceived by HCPs: relevant clinical trials (53% vs. 6%, respectively); NETs research (53% vs. 6%); psychological care (48% vs. 13%); signposting to patient associations (44% vs. 4%); advice on

management (34% vs. 1%). Only 16% of patients felt their needs for information about treatment options were fully met (vs. 41% of HCPs). Many patients use patient association (70%) or HCP (49%) websites for information, with 53% finding this fully/mostly meets their needs. No advocates felt that patient needs at diagnosis were fully met, and over 32% believed that appropriate standards of care were not met, particularly related to psychological (76%) and mental health (71%) care and holistic support (65%). Nearly all (94%) advocates reported MDTs were available in their region and 70% of HCPs said care was by MDT; however, only 66% of patients reported MDT access. Overall, 50% of patients felt fully/mostly involved in decision making. Access to Gallium-68-DOTATATE/DOTATOC PET/CT scanning (patients 72%; HCPs 86%; advocates 85%) and PRRT (42%; 77%; 95%) were considered key challenges. Half of patients (48%) reported travelling >300km/186 miles to see a specialist. Patient involvement in research was a priority (patients 53%; HCPs 57%; advocates 82%), with patients and advocates focussed on earlier, more accurate diagnosis and HCPs on clinical drug trials.

Conclusions: There are major gaps in fulfilling the informational needs of patients, providing access to gold-standard care, and involving patients in research.

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How to manage carcinoid syndrome

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Carcinoid syndrome is the result of advanced neuroendocrine tumours (NETs). The development of somatostatin analogues resulted in a major change in the management of patients with NET resulting in improved control of associated symptoms and ultimately disease control. Most patients do however develop recurrence or progressive symptoms (and disease) and thus alternate treatments are required. Alternatives will include interventions to control disease progression overall and new agents targeting symptoms specifically such as Telotristat ethyl. Novel interventions such as rose Bengal may also have a role in the future. Long term control of symptoms is crucial for quality of life but it is important to also consider prevention of carcinoid flare associated with surgical interventions and also PRRT. As PRRT access has increased clinicians increasingly understand the risk of symptom flare and new guidelines have been suggested and recently published.

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Management of pancreatic hormone syndromes

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Pancreatic neuroendocrine tumours arise from cells within the endocrine pancreas (Islets of Langerhans) and consequently may manifest symptoms relating to hormone secretion in addition to local tumour effects. Hormone production is determined by the tumour cell of origin (eg insulinoma from pancreatic beta-cells), and hormone hypersecretion may be fatal if uncontrolled. Tumours may also secrete more than one hormone. Consequently, effective management of functional pancreatic neuroendocrine tumours must control the hormone syndrome (symptomatic treatment) in addition to the underlying tumour (oncologic treatment). These therapeutic principles will be discussed, with a focus on symptomatic treatments for insulinoma, gastrinoma, glucagonoma, VIPoma, somatostatinoma and ectopic ACTH syndrome using case examples.

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Medical management for patients with well differentiated neuroendocrine tumors

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Neuroendocrine tumors (NETs) were previously thought be rare diseases where publications were frequently based on anecdotes, retrospective series, and small single arm studies. Prospective controlled clinical trials were rarely pursued leading to slow progress. Prior to 2011, streptozocin was the only FDA approved therapy for oncologic control and this limited to pancreatic NETs with many questioning its utility. Pivoting the field toward to one that is evidence-based and where rigorous controlled clinical trials are the norm have led to an explosion of new studies and treatment options. The completion of eight randomized controlled phase III studies have resulted in five FDA and six EMA approvals over the past seven years for oncologic control of NETs. Three placebo controlled phase III studies targeting carcinoid syndrome have resulted in two FDA approvals. While it has been difficult to demonstrate overall survival benefits in individual studies due to the number of patients needed, research using population based registries have shown improving overall survival especially among patients with advanced metastatic disease.

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Role of PRRT

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Details not available at time of publication.

Challenges of pre-operative and intraoperative management

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TBC

Surgical management

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Neuroendocrine Tumours [NETs] are a heterogeneous group of neoplasms with a highly variable biological behavior and clinical course. Most neuroendocrine tumours have a malignant potential on the basis of their ability to metastasize.

Surgery is one of the therapeutic options with a potential to cure localized disease and enable long-term survival in those with 'limited metastatic disease'. In the palliative setting, debulking can reduce the tumour burden and minimize the intractable symptoms of functional tumours thereby improving the quality of life and possibly survival.

The presentation will review the role of surgery in the management of these tumours with an emphasis on surgical techniques and principles.

Liver-directed PRRT and therapy

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Background : PRRT has emerged as treatment choice for inoperable or metastasized neuroendocrine tumors and this therapy seems more effective in the biochemical and volume control of disease than SSA or chemotherapy alone. Majority of the patients will have hepatic metastases at the time of presentation itself.

Aim: To demonstrate the efficacy and safety of Liver directed PRRT along with concurrent Chemotherapy (CAPTEM regimen in patients with well and moderately differentiated neuroendocrine tumors. Since Liver is a critical organ , delivery of PRRT to liver will result in higher dose and prolonged retention of isotope in the metastases, resulting in better outcomes.

Materials and methods: Patients with unresectable treatment refractory disease with normal liver and renal functions were treated using Lutetium 177 Dotatate. One hundred sixty two patients with well or moderately differentiated neuroendocrine tumors were evaluated. Ninety four patients with metastatic, unresectable or functioning tumors were treated with intravenous PRRT alone . Sixty eight patients were treated with Liver directed PRRT along with CAPTEM regimen.

Primary endpoint: Progression-free survival (PFS) from day end of PRRT to progression of disease or death was assessed using Kaplan Meier Analysis. Safety evaluation included incidence of nephro, hemato and hepatotoxicity during infusion and subsequent follow up period.

Results: The mean progression free survival with intraarterial PRRT with chemotherapy was 49.6 months (95% CI 5.5 to 38.8) compared to 12.9 months (95%CI 2.1 to 8.9) for IVPRRT alone (Log rank $\chi^2=42.1$, $p<0.001$). There were no toxicity events.

Conclusions: Procedure is well tolerated , safe and the data suggests encouraging results with liver directed PRRT and CAPTEM chemotherapy without significant toxicity.

Endoscopic treatment procedures

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Details not available at time of publication.

Pancreatic Neuro-endocrine tumors: Exploring the role of surgical management

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Publish consent withheld

Carcinoid heart disease - medical management

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Carcinoid heart disease (CHD) is a rare cardiac manifestation occurring in patients with advanced NENs and the carcinoid syndrome, usually involving the right-sided heart valves and eventually leading to right heart failure. The pathophysiology of CHD is still obscure and believed to be multifactorial. Patients with the rare diagnosis of CHD should be treated in specialized centres by a multidisciplinary team with experience in the treatment of this complex condition. Without a timely intervention, NET patients with CHD will eventually develop progressive right heart failure in parallel with a significant decrease in their life expectancy compared with those NET patients without CHD. Medical treatment includes firstly somatostatin analogues (SSA), based on NET cell ability to express specific somatostatin receptors on their surface membrane. Treatment with SSA improves the symptoms of CS as well as the negative haemodynamic impact of tumour vasoactive agents on CHD and on the development of heart failure. In the perioperative setting, continuous SSA infusion is of utmost importance, with a slow tapering down before treatment discontinuation. The SSA infusion is aimed at reducing serotonin release, optimizing surgical outcome by reducing perioperative complications such as hypotension, carcinoid crisis and death. Recently, telotristat etiprate, a novel serotonin synthesis inhibitor, has been reported as being highly effective for alleviating diarrhoea in patients with CS inadequately controlled by SSAs alone. This new drug may be promising for patients with CHD with intractably elevated levels of serotonin. Antihistamines to prevent flushing and bronchospasm, and corticosteroids to reduce bradykinin production may be used. The use of loop diuretics, together with fluid and salt, restriction and compression stockings, may initially relieve the symptoms of right heart failure. A better understanding of the molecular mechanisms underlying the progression of fibrosis in CHD may lead to the development of appropriate targets for targeted molecular therapy.

Carcinoid heart disease - surgical management

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Details not available at time of publication.

Challenging cases presentation

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Takotsubo cardiomyopathy – a case report in a patient with metastatic pheochromocytoma receiving steroids with Peptide Receptor Radionuclide Therapy (PRRT)

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Metastatic pheochromocytoma (MP) is a rare and complex condition. Management is twofold: controlling excess catecholamine secretion to minimise cardiovascular morbidity, and controlling tumour progression. We present a case of non-familial MP in a 55 yo man, ECOG 0. The original 6cm right adrenal pheochromocytoma was completely resected, with low volume, non-operable local-regional recurrence subsequently diagnosed. He was managed on phenoxybenza and atenolol but intermittently experienced severe cardiac symptoms due to catecholamine excess, requiring hospitalisation.

Upon biochemical progression and worsening blood pressure control, he was referred for Peptide Receptor Radionuclide Therapy (PRRT) with ¹⁷⁷Lutetium Octreotate (LuTate). Baseline echocardiogram was normal. Standard premedication (dexamethasone and ondansetron) was administered prior to his first therapeutic dose of LuTate. Within 24 hours, he suffered cardiovascular instability, severe hypertension and atrial fibrillation, requiring stabilisation at a tertiary ICU including adjustment of pharmacotherapy to prazosin and metoprolol. LuTate-induced catecholamine surge was presumed. He proceeded to make a complete recovery.

Prior to the second dose of PRRT, he received a variation in premedication (dexamethasone and palonosetron although LuTate was not administered. A rapidly developing hypertensive crisis again occurred, culminating in oliguria and acute pulmonary oedema. Plasma metanephrines rose to 17,813pmol/L (RR<900) with NT-Pro BNP 12,439ng/L (RR:0-124) with transthoracic cardiac echocardiogram demonstrating severe cardiac failure and apical hypokinesis. Aggressive therapy resulted in normalisation of the severe myocardial dysfunction.

Final diagnosis was of Takotsubo Cardiomyopathy, secondary to underlying MP and additional pharmacological triggers.

This case required cohesive, multidisciplinary care.

Key issues for review:

1. Understanding of potential crisis triggers, including exogenous corticosteroid administration and PRRT, in patients with MP
2. Optimal pharmacotherapy for prevention and treatment of hypertensive crises in patients with MP, in the absence of recognised guidelines.
3. Management of Takotsubo Syndrome including Beta blockade in patients with MP.

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New concepts in NEN pathology

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The WHO 2010 grading of GEP NENs used the G3 grade for neuroendocrine neoplasms (NEN) which have a Ki67 index of greater than 20%. It was assumed in the grading system that these neoplasms were poorly differentiated small cell or large cell neuroendocrine carcinomas (NEC). Tumours with well differentiated morphology were referred to as neuroendocrine tumours (NETs) which were further sub-graded as G1 or G2 based on their Ki67 labelling indices being 2 or <2 or 3-20 resp. It became apparent over the ensuing years that there were tumours which by virtue of their Ki67 labelling indices were NECs, but were not poorly differentiated and did not have the very poor outcomes associated with NECs. In the context of the GEP system, the pancreas was often the site of this anomalous situation. It was also apparent that lung tumour pathologists had been referring to G1 and G2 NETs as carcinoids, while using the term atypical carcinoid for a group which were morphologically close to carcinoids but had a higher mitotic rate. The carcinoid group was distinct from small cell or large cell neuroendocrine carcinomas. Meanwhile, data from molecular analysis of NENs lent support to the growing realization that NETs and true NECs should not be separated by proliferation criteria alone. They were molecularly and biologically separate entities, and that NET G3 exists as a well differentiated NEN with a higher proliferation index than NET G2. The new clinico-pathological insights that have led to the current understanding of NEN G3 will be highlighted in the talk.

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Challenges and Treatment options for patients with Grade 3 GEP NEN 'Medical Management + PRRT

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High-grade gastroenteropancreatic neuroendocrine neoplasms (WHO 3) have a Ki-67>20% and are well-differentiated neuroendocrine tumors (NET G3) or poorly-differentiated neuroendocrine carcinomas (NEC). NEC originate anywhere in the gastroenteropancreatic tract, whereas NET G3 are mainly pancreatic and have a much better prognosis than NEC.

An aggressive approach is scheduled with localized disease as many can be cured. Adjuvant therapy is recommended after radical surgery of NEC. Metastatic NEC is usually treated with platinum-based chemotherapy and etoposide, with a response rate of 30-40%, progression-free survival 4-6 months and median survival 8-13 months. No differences are seen comparing cisplatin- to carboplatin-based chemotherapy. Neoplasms with a Ki-67<55% are less responsive to platinum-based chemotherapy, but have a significant longer survival. Small studies show some benefit of 2nd-line chemotherapy. NET G3 patients do not respond to platinum-based chemotherapy and other treatment alternatives should be considered. PRRT may be an evolving therapy in selected NEN G3 patients.

Peptide receptor radionuclide therapy (PRRT) in ENETS Grade 3 (G3) Neuroendocrine Neoplasia (NEN) - a single-institution retrospective analysis

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Aim

Grade 3 NENs are aggressive tumours with poor prognosis. PRRT +/- radiosensitising chemotherapy is a potential treatment for disease with high SSTR-expression without spatially discordant FDG-avid disease. We retrospectively evaluated the efficacy of PRRT in G3 NEN.

Materials & Methods

All patients with G3 NEN (Ki-67>20% on immunohistochemistry) and who had completed at least one cycle of PRRT between January 2005 and January 2017 were retrospectively reviewed.

Kaplan-Meier estimate was used to determine progression free survival (PFS) and overall survival (OS) defined from start of PRRT. Subgroup analysis was performed for patients with Ki-67≤55% and >55%.

Anatomical response (CT RECIST 1.1) and toxicity 3 months after PRRT was determined. Disease control rate (DCR) was defined as complete response (CR), partial response (PR) and stable disease (SD) of those with prior progression.

Results

28 patients (M=17; age 16-78 y.o; Ki-67≤55%=22) were reviewed. 17 patients had pancreatic, 5 small bowel, 3 large bowel, 2 bronchial and 1 unknown primary disease. 25/28 had significant FDG-avid disease prior to treatment. Most had ¹⁷⁷Lu-DOTA-octreotate (median cumulative activity 24.4 GBq, median 4 cycles). 20 had radiosensitising chemotherapy. 89% were treated for disease progression; 79% after prior chemotherapy.

Median follow-up was 29 months. The median PFS was 9 months for all patients. 16 patients died (Ki-67≤55%=11; Ki-67>55%=5) with median OS of 19 months. For Ki-67≤55% (N=22), the median PFS was 12 months and median OS 46 months. For Ki-67>55% (N=6), the median PFS was 4 months and median OS 7 months. On CT imaging, DCR at 3 months post PRRT was 74%; 35%(8/23) PR and 39% (9/23) SD. Grade 3 and 4 thrombocytopenia occurred in five patients. No renal or liver toxicity related to treatment was seen.

Conclusion

PRRT achieves clinically-relevant disease control with acceptable toxicity in G3 NENs.

Identification and characterization of novel markers in high grade neuroendocrine tumor cells

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Introduction:

Neuroendocrine tumors (NETs) are uncommon neoplasms that arise from the cells of endocrine and neural origin. They are heterogeneous in nature and showcase a range of biological activity. High grade tumors, known as Neuroendocrine Carcinomas (NECs) are rare and aggressive cancers that are generally rapidly fatal. Early diagnosis of the disease will require the identification of reliable biomarkers. This project is part of the randomised clinical trial (NABNEC) of Nanoparticle Albumin Bound Paclitaxel (NAB-Paclitaxel) with carboplatin in Gastrointestinal NECs aiming to understand markers characteristic of NECs that have not been extensively studied.

Methods:

Markers of differentiation, proliferation, cell adhesion and metastasis were selected from literature. Expression profile of these markers at mRNA and protein levels were conducted on 2 tissue samples of pancreatic and small intestine origin, using Real time PCR and immunohistochemistry. The expression level of the markers in the tumor were studied in comparison to the control samples from each patient. This will be extended to NEC specimens from several national biobanks and NABNEC patients and later the expression profile correlated with clinical endpoints.

Progress:

Based on the expression profile of the pancreatic and small intestine samples, markers of differentiation like CD31, CD44 showed significant increase in expression in the tumor samples compared to normal. Also, some markers like laminin, synaptophysin, CK7 and CK20 showed difference in expression levels between tumor samples of different origin. Changes in the levels of expression of these markers will be correlated with clinical data.

Conclusion:

This study will improve diagnostic procedures to better reflect the heterogeneity of the disease. It will also provide information about the cell biology of neuroendocrine tumors. Extending this study to a larger cohort will lead to a more population relevant conclusion.

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Challenges and management of NETs from other origins ‘ Pulmonary NET, Unknown primary

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Pulmonary well-differentiated neuroendocrine tumors are classified as either typical carcinoids (TC) or atypical carcinoids (AC) based on morphology, mitotic count and the presence or absence of necrosis. They represent 1-2% of pulmonary neoplasms and approximately 25% of all neuroendocrine tumors. At diagnosis, the vast majority are sporadic, non-functioning and typical carcinoids (TC to AC ratio 8:1). They are often diagnosed at an early stage and resected radically with a good prognosis. No adjuvant therapy is recommended after radical surgery. Everolimus constitutes the only approved drug for use in the metastatic setting, whereas somatostatin analogues, cytotoxic chemotherapy and peptide receptor radionuclide therapy are also used.

Well-differentiated NETs of unknown primary site are usually approached similarly to well-differentiated NETs of the gastrointestinal tract. They behave similar to metastatic small- intestinal NET with regard to survival. Depending upon the clinical situation, appropriate management may include local therapy or systemic therapy as somatostatin analogs, PRRT or cytotoxic therapy.

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PPGL - imaging and theranostics

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Pheochromocytomas (PCCs) and paragangliomas (PGLs) are rare chromaffin cell tumors (PPGLs) that raise significant challenges in clinical recognition, diagnosis and therapy, and when under-diagnosed could associate with severe morbidity. Recent discoveries in PPGLs genetics improved our understanding in the pathophysiology of tumorigenesis and allowed the application of functional classification of pathogenetically distinct groups of PPGLs. Given the overexpression of a wide variety of specific targets in PPGLs, it seems that these tumors are optimally suited to be imaged by specific radiopharmaceuticals. For most of the cases, one or more molecular (functional) imaging methods are employed, such as 123I-MIBG scintigraphy, 18F-FDG or 18F-DOPA PET/CT, or somatostatin receptor imaging. The selection of the functional modality could be based on knowledge of the patient's genetic background. The definitive treatment of PPGL is surgical excision of the tumor. However, in patients with progressive and widely metastatic PPGLs, the therapeutic options were limited until recent years to traditional chemotherapy using cyclophosphamide, vincristine, and dacarbazine (CVD), usually tolerated for long periods but with limited efficacy together with important side effects. Experience with other chemotherapeutic agents such as temozolomide is limited, whereas new data on several TKIs with mainly anti-angiogenic activity seem promising. Theranostics approaches using high-specific activity MIBG or peptide receptor radionuclide therapy (PRRT) with radiolabeled somatostatin agonists are rapidly evolving in the setting of these tumors and are considered as a breakthrough in the therapeutic arsenal of metastatic PPGLs.

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Genomics and immunogenomics of Merkel Cell Carcinoma

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Details not available at time of publication.

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Overview, management and novel treatment approaches to Merkel Cell Carcinoma

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Details not available at time of publication.

Biliary Mixed Neuroendocrine-Nonneuroendocrine Neoplasms: a series of four cases with review of literature

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Background

Mixed Neuroendocrine-Nonneuroendocrine Neoplasms (MiNENs) are rare tumors comprising of both adenocarcinoma and neuroendocrine component, at least 30% of each in the lesion. We report 4 biliary MiNENs, with a brief literature review.

Case 1: 22 year old male with jaundice had distal bile duct MiNEN, and a single DOTA positive liver lesion. He underwent neoadjuvant 4 cycles FOLFOX followed by pancreaticoduodenectomy (PD).

Case 2: 65 year old male came post-laparoscopic cholecystectomy with biopsy suspicious of adenocarcinoma. Patient underwent completion radical cholecystectomy which revealed an infiltrating GB MiNEN. Patient is on Cisplatin + Etoposide.

Case 3: 51 year old male presented with endoscopic ampullectomy for periampullary lesion - MiNEN arising from distal bile duct. Patient was taken for PD, abandoned due to dense adhesions to major vessels. He was given 3 cycles of FOLFIRINOX followed by surgery followed by 2 cycles of Cisplatin + Etoposide, later changed to 4 cycles of Gemcitabine + Capecitabine due to poor response. He responded well, and is disease free at 14 months.

Case 4: 35-year old lady with painless jaundice had a mid-bile duct stricture. Endoscopic Ultrasound guided Fine Needle Aspiration Cytology (EUS-FNA) revealed neuroendocrine differentiation. She underwent margin-negative extrahepatic bile duct resection that was a MiNEN. She was given 6 cycles of capecitabine + temozolomide, and is disease free at 2 years.

Conclusion

Biliary MiNENs don't have a dedicated treatment approach as of now. Treatment for resectable tumours is upfront surgery, but advanced tumours can be downstaged with chemotherapy and then resected. Survival in MiNENs is generally poor, and response to chemotherapy is modest.

Genetics landscape in NETs

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Current and upcoming trials

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Neuroendocrine tumors (NETs) were previously thought to be rare diseases where publications were frequently based on anecdotes, retrospective series, and small single arm studies. Prospective controlled clinical trials were rarely pursued leading to slow progress. Prior to 2011, streptozocin was the only FDA approved therapy for oncologic control and this limited to pancreatic NETs with many questioning its utility. Pivoting the field toward to one that is evidence-based and where rigorous controlled clinical trials are the norm have led to an explosion of new studies and treatment options. The completion of eight randomized controlled phase III studies have resulted in five FDA and six EMA approvals over the past seven years for oncologic control of NETs. Three placebo controlled phase III studies targeting carcinoid syndrome have resulted in two FDA approvals. While it has been difficult to demonstrate overall survival benefits in individual studies due to the number of patients needed, research using population based registries have shown improving overall survival especially among patients with advanced metastatic disease.

Emerging combination therapies with PRRT

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Details not available at time of publication.

NEN perspective in China

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Over the past four decades, the incidence of NENs has significantly increased 6.4 folds from 1.09/100,000 to 6.98/100,000 according to the SEER database. There are still no epidemiological data of NENs based on population in mainland China.

Gastroenteropancreatic Neuroendocrine Neoplasms (GEP-NENs) is the most common type of NENs which account for 65%-75% of NENs from all sites. However, among different ethnicities and regions, the most common primary sites are different. In mainland China, the top 3 sites of GEP-NENs are pancreas, rectum and stomach, while small intestinal NEN is much rarer.

Treatment of NEN patients should be an individualized and multidisciplinary comprehensive management. However, in mainland China, most of the physician lack a thorough understanding of NEN and they often refer these patients to different departments. NEN patients were handled respectively by each specialized department before 2010. Chinese doctors started to pay attention to NENs since 2010 when nomenclature and classification of neuroendocrine tumors of digestive system were updated by WHO. Thereafter, pathologists in China successively reached two consensuses on pathological diagnosis of GEP-NEN which were published in 2011 and 2013 respectively. In clinical practice, some large medical centers successively started to set up neuroendocrine neoplasm multi-disciplinary team (NEN-MDT). Various medical associations (including the disciplines of gastroenterology, oncology, and pancreatic surgery) have released several related guidelines/consensuses for NENs respectively.

Moreover, increasing number of experts from NEN- related disciplines and fields have gradually gathered together and founded several professional NEN study groups/ associations. Based on these cooperating platforms, experts with a common goal set about establishing NEN databases, carrying out multi-center clinical trials and basic studies, and formulating expert consensus for point-to-point implementation.

Mission and Vision for APNETs

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The Asia Pacific Neuroendocrine Tumour Society [APNETs] is a relatively young regional professional society devoted primarily towards improving the management of neuroendocrine tumours through education, awareness, and research. The society's scientific meetings are important educational and training activities during which experts from around the world share their expertise and knowledge on current developments in this relatively uncommon disease.

The presentation will touch on the mission and vision of the society and its future direction.

International collaboration of NET societies - challenges, goals, with focus on patient unmet needs

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A case of appendiceal goblet cell carcinoid tumour

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Introduction:

Goblet cell carcinoid (GCC) is a rare neoplasm of the vermiform appendix. A histopathological examination is vital as there are no obvious macroscopic features identifiable during surgery for a "suspected appendicitis". Due to its rarity, it may be misinterpreted as neuroendocrine tumor.

Case Report:

We report a 37-year-old male diagnosed histopathologically as appendiceal neuroendocrine tumour after undergoing an appendectomy when he presented with acute appendicitis. He was referred to our institution for further management of NET.

Re-examination of the slides by our histopathologist reported the specimen as a mixed neuroendocrine-non-neuroendocrine neoplasm (MiNEN) of intermediate grade (goblet cell carcinoid) as there were two morphologically distinct tumour components. The conventional group, composing of nests and cords of tumour cells, exhibited round uniform nuclei with salt and pepper chromatin and scanty eosinophilic cytoplasm (NET appearance). The second group of cells displayed irregular infiltrating nests of goblet cells with abundant univacuolated cytoplasm and peripheral compressed nuclei. Both tumour groups encompass >30% of tumour volume each. Mitotic figures were not seen. Immunohistochemical studies showed both tumour groups being positive to synaptophysin and chromogranin. Only the goblet group shows positivity to CK20. Ki-67 proliferation index is <2%.

Based on the HPE we classified the patient as Tang's classification group A (classic GCC). He decided to undergo right hemicolectomy subsequently and the histopathological examination showed no local invasion. The patient is currently well postoperatively and is scheduled for a FDG-PET scan for further staging.

Conclusion:

GCC tumours are more aggressive than classical neuroendocrine tumours even if they do not exhibit malignant properties of adenocarcinomas. Thus, they should be identified promptly as their further definitive therapy differs from adenocarcinoma or NETs.

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Neuroendocrine neoplasm trends over 32 years in Queensland, Australia

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BACKGROUND: The Incidence of Neuroendocrine neoplasms (NENs) has been increasing worldwide. This retrospective population-based analysis describes demographics, incidence and mortality of NENs across Queensland.

METHODS: Patients diagnosed with NENs were obtained from the Queensland Oncology Repository. Findings include the overall and site-specific incidence, mortality and cause specific survival.

RESULTS: 4,484 NENs were diagnosed between 1982 and 2014. The median age was 56 years and 54% were females. Almost one third (30%) resided in rural areas. The incidence of NENs increased from 1.4 cases to 6.7 cases per 100,000 over the 32 year period. Despite the increase in incidence, mortality rates have remained low, from 0.3 cases in 1982 to 0.5 cases per 100,000 in 2014. NENs were most commonly diagnosed in the appendix (26%) lung (19%), small intestine (19%) and rectum (14%), comprising 79% of all cases. However, over the last 5 years NENs diagnosed in the small intestine have increased in incidence and become the second most common primary site after appendix. The incidence of primary site presentation varied depending on gender and age group. Cause specific 5year survival from 1982-1986 was 76% (95% [CI 71.0, 82.0], 1995 – 1999 was 83.1% (95% [CI 79.7, 86.6]) and in the years 2010 – 2014 further improved to 93.0% (95% [CI 91.3, 94.9]). Over 50% of patients are still living 20 years after diagnosis. Survival also varied by primary site, the highest being for rectum and appendix, and poorest in NEN of unknown primary site and pancreas. Individuals >61 years also had poorer survival.

CONCLUSION: The incidence of NENs in Queensland is rising and there is variation in primary site distribution. Survival from NENs is improving, consistent with studies worldwide.

Retrospective analysis of systemic chemotherapy for poorly differentiated extra-pulmonary neuroendocrine carcinoma

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This study was performed to determine the outcome of systemic chemotherapy for extra-pulmonary poorly differentiated neuroendocrine carcinoma (NEC). Clinical data from 41 patients with unresectable or recurrent NECs, who received systemic chemotherapy, were collected from Chonnam National University Hwasun Hospital and analyzed retrospectively.

Patients had primary sites in the gut (n=17), pancreatoco-hepatobiliary system (n=15), genitourinary (n=4), head and neck (n=3) and other sites (n=2). Etoposide plus cisplatin (EP) was most commonly selected for first line chemotherapy. For patients treated with EP, the response rate was 42.5%, median progression free survival (PFS) was 7.4 months, and median overall survival (OS) was 13.7 months. 53% of patients (n=22) were received second line chemotherapy. For patients treated with second-line chemotherapy, Irinotecan plus cisplatin (IP) was most commonly selected, the response rate was 9.5%, median progression free survival (PFS) was 3.0 months, and median overall survival (OS) was 6.8 months.

A randomized controlled trial is required to establish the appropriate chemotherapy regimen for extrapulmonary poorly differentiated NEC.

The impact of SSTR2 expression in patients with metastatic GEP-NETs receiving somatostatin analogs

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Background: Among the five subtypes of somatostatin receptor (SSTR1–5), the anti-proliferative effects of somatostatin analogs have been linked to their affinity for SSTR2. Thus, SSTR2 can be used as both a diagnostic and a therapeutic target in patients with gastroenteropancreatic neuroendocrine tumor (GEP-NET).

Methods: We evaluated SSTR2 expression by immunohistochemistry (IHC) using tumor samples of 20 GEP-NET patients receiving somatostatin analogs and its impact on the tumor response to somatostatin analogs and patient survival.

Results: Primary sites included 15 foregut-derived GEP-NETs [stomach (n = 3), duodenum (n = 4), biliary tract (n = 3), and pancreas (n = 5)] and 5 hindgut-derived GEP-NETs of the distal colon and rectum. Among the 20 patients, 13 (85.5%) exhibited expression of SSTR2 in tumor tissues. Expression of SSTR2 was significantly associated with low-grade WHO classification (p = 0.007), but not with gender, primary site, or number of metastatic sites. Disease control rate was superior in patients with SSTR2 positivity compared to patients with SSTR2 negativity. Moreover, the status of SSTR2 expression could significantly predict longer PFS (positive, not reached vs. negative, 2.1 months; p = 0.001).

Conclusion: SSTR2 expression had both predictive and prognostic value for survival of patients with metastatic GEP-NET receiving somatostatin analogs.

AGITG NABNEC: A Randomised Phase II Study of Nab-Paclitaxel In Combination With Carboplatin As First Line Treatment Of Gastrointestinal Neuroendocrine Carcinomas

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Background: Neuroendocrine carcinomas (NEC WHO grade 3) are rare aggressive cancers. There are no randomised trials to date to establish standard therapy for advanced gastrointestinal (GI) NECs. Standard practice is to treat GI-NECs with etoposide and carboplatin. Paclitaxel is also active in NECs however there is no data on the role of nab-paclitaxel. NABNEC aims to establish if the carboplatin and nab-paclitaxel combination is an effective and tolerable treatment for advanced GI-NECs and to enhance our understanding of the biology and imaging characteristics of NECs. **Methods:** DESIGN: Randomised, non-comparative, stratified, multicentre phase 2 trial. Primary endpoint (n=70): objective response rate (RR) by RECIST 1.1 at 6 months. Secondary endpoints: progression free survival, overall survival, adverse events by NCI-CTCAE V4.03 and quality of life (EORTC QLQC30, QLQ-GINET21 questionnaires). Translational endpoints include 1) blood and tissue biomarkers (prognostic and/or predictive) correlated with clinical endpoints including circulating tumour cells, mutation profile, DNA methylation profile; 2) correlation of 18-fluoro-deoxyglucose positron emission tomography (FDG-PET) to early response and other clinical endpoints. SAMPLE SIZE: 70 patients gives 80% power and 95% confidence to rule out a 30% RR in favour of a clinically relevant RR of 50% at 6 months. POPULATION: Adults with advanced non-resectable GI-NEC (includes small cell and large cell NEC). TREATMENT: Randomisation 2:1 to Arm A nab-paclitaxel 100 mg/m² on Day (D) 1 weekly and carboplatin AUC=5 on D1, 3 weekly; and Arm B IV etoposide 100mg/m² on D1-3, and carboplatin AUC=5 on D1, 3 weekly until disease progression or unacceptable toxicity. ASSESSMENTS: ⁶⁸Ga Octreotate PET at baseline, CT scan at baseline and every 9 weeks, FDG PET at baseline, 9 weeks then every 18 weeks and QOL questionnaires every 9 weeks until disease progression. NABNEC has so far enrolled 17 patients at 15 sites in Australia. ANZCTR # 12616000958482

Nutritional status and considerations for patients diagnosed with a gastroenteropancreatic neuroendocrine tumour: preliminary baseline characteristics from the Nutrition in NETs study

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Background

Gastroenteropancreatic neuroendocrine tumours (GEP NET) cause various symptoms impacting on nutritional status and diet. Published data indicates up to 25% of GEP NET patients are malnourished, and dietary change is prevalent. Nutrition in NETs is a prospective longitudinal study aiming to describe the impact of GEP NETs on patient's nutritional status and quality of life. Baseline characteristics of study participants are discussed.

Methods

Patients diagnosed with a GEP NET were recruited upon initial attendance to the Peter MacCallum Cancer Centre (Melbourne, Australia). Recruitment commenced in July 2017 and is ongoing. At baseline, participant demographics and patient-reported outcome data was recorded (dietitian contact, dietary habits, and symptoms). Nutritional status was measured using the patient-generated subjective global assessment (PG-SGA).

Results

Fifty two patients were approached and 47 recruited over 8-months thus far. Sixty six percent were male: average age was 59 years. Tumour grading varied (24% NET G1, 33% NET G2, 22% NET G3). The majority were diagnosed with a primary site of small bowel or pancreas (43% and 36% respectively) and had metastatic disease (77%, n=36). Thirty percent were malnourished, and only 21% (n=10) reported contact with a dietitian. Fifty seven percent had changed their diet since diagnosis.

Conclusion

The recruited patients represent a heterogeneous sample, consistent with published literature. Results highlight malnutrition and dietary change as prevalent and potentially under-recognised factors for consideration in the management of GEP NET patients. Longitudinal data is being collected in this patient cohort to explore change in nutritional status and dietary habits over time.

Exploring nutrition screening and management practices amongst health professionals managing patients with neuroendocrine tumours

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Background

Patients with neuroendocrine tumours (NET) are at nutritional risk due to symptoms and side-effects of treatment. Current evidence based guidelines lack information regarding optimal nutritional management and supportive care. This study aims to describe current knowledge and management of nutrition complications in NET patients.

Methods

Health professionals regularly managing NET patients were invited by email to participate in a 21-item online survey. Demographic information was recorded and included country of work, profession and length of time working with NET patients. Questions asked about symptom prevalence, their impact in NET patients, and nutrition screening and assessment practices. Preliminary results were summarized.

Results

Of the 61 health professionals who completed the survey, 36 (59%) worked in Australia and 13 (21%) worked in the United Kingdom. Professions represented included medical oncologists (28%), nurses (25%) and dietitians (23%). Fifty percent reported managing NET patients for more than 7 years. Diarrhoea and fatigue were reported as the most common and of concern symptoms amongst NET patients. Provision of advice on symptom management, weight loss and food intolerances was reported by 90%, 52% and 34% respectively. Screening for malnutrition and vitamin deficiencies was reported by 34% and 36% respectively. Barriers to screening included limited knowledge of appropriate screening practices, and belief the role of screening aligned with another profession.

Conclusion

Reported symptom prevalence and burden appears to align with published patient reported data. There is variation in reported methods of malnutrition screening and assessment, and management of symptoms is more common practice than malnutrition or vitamin screening among NET health professionals. This is the first summary of the nutrition practices of NET health

professionals. Further research is required to guide optimal nutrition screening practices and contribute to the development of nutrition guidelines for NET patients.

Living with a rare and complex cancer diagnosis: Describing the experiences, information and supportive care needs needs, psychosocial status and characteristics of patients with newly diagnosed Neuroendocrine Tumours

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Publish consent withheld

Renal tubular injury presenting after 177Lu-DOTATATE peptide receptor radionuclide therapy with high renal dosimetry

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177Lu-DOTATATE (LuTATE) peptide receptor radionuclide therapy (PRRT) is increasingly used and shown to have low risk of renal toxicity(2), such not seen in the prospective NETTER-1 trial (1). There is paucity of human renal studies, however rodent models of LuTATE nephrotoxicity showed damage occur at a dose-dependent fashion in the proximal tubules continuing to more distal tubules (3), and renal toxicity becoming clinically overt 100-200days afterwards(4).

We present a case of a 58 year-old Caucasian with metastatic small bowel neuroendocrine tumour, who was treated with cumulative administered dose of 33GBq of over standard 4 cycles, who developed decline in renal function from baseline GFR of 65ml/min/1.73sqm to stage 4 CKD (eGFR ranging 17-29ml/min/1.73sqm.) evident only 3-6 months after completion of LuTATE. Patient also developed progressively worsening macrocytic anaemia becoming transfusion dependent despite erythropoietin, with bone marrow aspirate showing hypocellular marrow.

Renal biopsy showed relatively acute tubular injury, predominantly in the proximal tubules, with background mild tubular atrophy, interstitial fibrosis, focal moderate arteriosclerosis and ischaemic glomeruli (patient has history of hypertension).

We postulate that the renal tubular injury is related to PRRT, given absence of any other causes that could lead to such persistent stepwise decline in renal function, this is despite satisfactory pre-cycle eGFR that ranged between 58-83ml/min/1.73sqm, that many centres would have treated with standard cumulative dose.

We will show that this patient's routine post-cycle 1 renal dosimetry showed a renal absorbed dose of 12.6Gy(1.58Gy/GBq), which in retrospect is higher than our contemporaneous cohort of 50 patients with post-cycle 1 dose of 5.4+/-2.1GBq (mean +/-SD).

We will contend that LuTATE renal dosimetry should be universally performed as more patients are being treated, so that more data can be collected from major centres and analysed to better inform a more appropriate renal dose upper limit for LuTATE.

Peptide receptor radionuclide therapy (PRRT), a promising therapy in adrenocorticotrophic hormone (ACTH) producing metastatic neuroendocrine tumour (NET).

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Background

Ectopic adrenocorticotrophic hormone (ACTH) producing neuroendocrine tumours (NETs) are a rare entity, with a reported incidence of approximately 3%. Detection and excision of isolated primary tumours is the mainstay of treatment. In metastatic disease, patients who progress despite medical therapy or those with intractable Cushing's syndrome would usually succumb to bilateral adrenalectomy. There is an increasing role of peptide receptor radionuclide therapy (PRRT) in NETs due to its

favourable safety profile and treatment outcomes. There is limited literature describing the utility of PRRT in hormonal and tumour control in ACTH-producing NETs.

Methods

Outcome of 3 consecutive patients with ectopic ACTH secreting metastatic NETs treated with PRRT at PMCC were retrospectively reviewed.

Results

Patients one (2 mitosis/10 hpf) and two (Ki-67 15%) had metastatic gastrinoma, patient three had metastatic rectal NET (Ki-67 >95%). Patient 1 required bilateral adrenalectomy, followed by PRRT due to persisting hormone secretion, which resulted in biochemical and complete imaging response sustained nine years following the last cycle. Patient 2 received PRRT with concurrent Metapyrone blockade; the 1st cycle was complicated by tumour lysis and transient biochemical deterioration with subsequent cycles better tolerated, and resulted in sustained biochemical and near-complete imaging response of 27 months duration, avoiding adrenalectomy. Patient 3 was referred with progressive high grade metastatic rectal NET, despite two lines of chemotherapy. He received 2 cycles of PRRT with adrenal blockade which conferred a short interval of biochemical and disease response, however the disease rapidly progressed with spatial discordance (FDG +ve / SSTR -ve), with the patient deceased 3 months after commencement of PRRT.

Conclusion

This small series highlights the potential role of PRRT in biochemical and tumour control in ACTH-secreting NETs with ongoing response seen in two of three patients with high SSTR-expressing tumours.

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A 41 year old patient with abdominal sepsis from neuroendocrine tumour misdiagnosed as pelvic inflammatory disease

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Neuroendocrine tumors are slow-growing epithelial tumors with predominant neuroendocrine differentiation. Being a rare form of neoplasm they are frequently not considered in the differential diagnosis. Clinical manifestations are often non-specific and may include abdominal pain, bowel obstruction, diarrhoea, weight loss and gastrointestinal bleeding. Here we present a case of a 41-year-old woman with non-specific abdominal pain. During multiple hospital presentations she was misdiagnosed with infectious pelvic inflammatory disease and treated ineffectively with antibiotics when the underlying condition of her persistent abdominal pain was a mid-gut neuroendocrine tumor that had caused bowel perforation and formation of an abscess in the pouch of Douglas.

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Virilising Adrenal Tumor in 20 yrs Hirsute Female - A Case Report

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A 21yrs old female came to endocrine department of Bangabandhu Sheikh Mujib Medical University with complained of hirsutism with male body habitus, male pattern voice since her 12yrs of age. She had primary amenorrhoea. She was sent to National Institute of Nuclear Medicine & Allied Sciences for ultrasonography (USG) of whole abdomen. A big complex mass was detected at superoposterior aspect of her left kidney with small sized uterus (AP-1.1cm, L- 3.8cm) and very small ovaries (streak ovary). Preoperative evaluation showed serum dehydroepiandrosterone (DHEA sulphate level >1000µg/dl (1.3 - 9.8ng/dl), testosterone was 451ng/dl (63-120ng/dl), cortisol level was 340.8 nmol/L (138 - 690 nmol/L), 24hrs urinary vanillylmandelic acid (VMA) 13.06 ng/day, Karyotyping showed 46XX. Patient underwent laparoscopic left adrenalectomy; the mass was removed from abdomen. Histopathology report showed adrenocortical neoplasm. Postoperative evaluation was done 4 months later. Report showed that serum DHEA 12.20 ng/dl, serum testosterone level 17.9ng/dl, serum cortisol 705 nmol/L, 24 hrs urinary VMA 7.08ng/day. USG of whole abdomen showed uterus (AP-2.3cm, L-5.8cm) and ovaries become normal, kidneys were normal, other abdominal organs showed normal findings. Patient was treated by estrogen 0.6mg once daily for 21 days, [Medroxyprogesterone](#) tablet 10 mg for 7 days these drugs were continuing for 6 months. Tab spironolactone (50mg) once daily at same duration. Testosterone was again done 1yr after adrenalectomy it was 88.2 ng/dl, Serum cortisol 199 nmol/L. Patient gonadotrophine and sex hormones level was normal. She was conceived 4yrs after this treatment but miscarriage occurred. Her hirsutism was completely cured. Now she was under the treatment of the gynecologist. In ending a successful normalization of reproductive organs as well as rapid decreased of rising hormones level was monitored in this patient.

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Punching above its weight - The Australasian Merkel Cell Carcinoma Patient Advocacy Group

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Merkel cell carcinoma (MCC) is an aggressive neuroendocrine skin cancer with a mortality rate 3x that of melanoma. Despite being a rare cancer, Australia has the highest incidence in the world, twice that of Europe and US. Those suffering from MCC are often elderly, with comorbidities precluding traditional aggressive therapy. Life-expectancy is low, there are no established therapeutic frameworks, and clinical trials are recommended as standard-of-care. Due to its rarity, patients/carers often have limited means of support.

To respond to this, the Australasian MCC Patient Advocacy Group (AMPAG) was formed as part of the Australasian MCC Interest Group (AMIGOs); both supported by the Australia and New Zealand Melanoma Trials Group. Consisting of patients/carers affected by MCC, AMPAG connects sufferers and helps focus the efforts of AMIGOs, ensuring patient voices are heard.

AMPAG has already provided vital research input into new MCC trials in development. It is establishing a website with links to related groups and convened two meetings in its first six-months of existence. The AMPAG Chair recently was first-speaker in a pharmaceutical adboard meeting, the first time a patient advocate had done this on behalf of patients with any cancer, and means that patients are represented in discussions. A letter sent to the Therapeutic Goods Administration, signed by an AMPAG representative, led to approval of a promising immunotherapy drug as first-line treatment for advanced MCC. AMPAG was also represented at the AMIGOs' first educational symposium, conducted to educate healthcare professionals (HCPs) about MCC treatment options.

AMPAG is punching above its weight, having achieved many 'firsts' in its short life. With an active advocate as chair of this group, AMPAG continues to advocate for patient-focused priorities like lobbying for free PET scans, listing of effective drugs on the Pharmaceutical Benefit Scheme, and increasing education to HCPs/patients/carers – watch this space!

A new era in the optimal planning of treatment and research of Neuroendocrine tumours (NETs) in Australia: the PLANET registry

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NETs are uncommon (6–10:100,000) and complex neoplasms. The PLANET registry (www.planet.org.au) has been instigated to address the rise in incidence and the lack of a national NETs registry, that will allow patient data to be systematically collected and curated in order to better understand NETs.

The aim is to create an Australia-wide clinical registry for NETs, that will collate key data to evaluate patient outcomes leading to valuable improvements in clinical practice, health outcomes, and facilitate collaborative research. This Registry will also give patients a unique opportunity to directly contribute to specific data collection.

The *PLANET* registry has a unique multi-disciplinary approach with active participation of oncologists, endocrinologists, gastroenterologists, surgeons, nuclear medicine physicians, pathologists, radiologists, specialist nurses and consumers, that operates as a committee, supported by a targeted security-oriented web-platform developed by the Melbourne eResearch Group. *PLANET* has established a descriptive, multi-centre, observational, retrospective and prospective, non-interventional, open-ended surveillance registry. Patients are empowered to contribute to this registry through accompanying privacy-protecting mobile applications (apps). This enables patients to enter data on their quality of life (QoL), Bristol Stool Scale, Weekly Vitals (weight, height, BMI) and ECOG score, as well as receiving notifications from doctors via the registry.

PLANET is in the process of ingesting data from major cancer centres across Australia. The registry data model has been standardised by the *PLANET* steering committee. Initial interrogation of the registry resulted in a number of summary data. Examples will be demonstrated at the meeting.

Uncommon tumours such as NETs are understudied, and not well understood in terms of their biologic and clinical characteristics. NETs have significant impact on patients due to their long disease course, with significant chronic morbidity and impaired QoL. *PLANET* has the potential to enhance our understanding of NETs, foster collaborations, clinical-trial participation, and make a mark internationally.

Adrenocortical carcinoma presenting with combined hypersecretion of adrenal steroid hormones.

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A 62-year-old female presented to the emergency department with severe hypertension. Further questioning revealed a four-month history of low mood, poor concentration, lethargy and proximal weakness. She also reported a 10kg weight gain and new facial hirsutism over the preceding year.

On examination she was hypertensive (BP 215/99mmHg) on four antihypertensives with subtle cushingoid features. She demonstrated slight facial plethora, mild proximal myopathy, mild dorsocervical and supraclavicular fat-padding. There was no abdominal striae or appreciable abdominal masses. She had features of hyperandrogenism with Ferriman and Gallway scores of 3 and 2 at lip and chin respectively.

Biochemistry demonstrated marked hypokalaemia with potassium of 2.9mmol/L and an aldosterone level was 120pmol/L (<978), with a renin level of 15mIU/L (4.4 – 46) and a ratio of 8 (<70) (while taking interfering medications). Catecholamines and metanephrines were normal.

Total testosterone was markedly elevated to 7.0nmol/L (0.2 – 1.8), with DHEA-S and androstenedione levels on the upper limit of normal at 10umol/L (1.0 – 11.7) and 12.9nmol/L (1.0 – 12.9) respectively. Cortisol precursors were elevated with an 11-deoxycortisol level of 4.8nmol/L (0.2 – 4.6). Diurnal variation in cortisol secretion was lost with fasting levels from 1162-1281nmol/L and evening levels between 693 -1058nmol/L.

CT and MRI scans demonstrated a large bilobed right adrenal mass measuring 6.4 x 4.9 x 5.8cm with diffusion restriction increasing the likelihood of a malignant lesion/adrenal carcinoma.

She proceeded to an open adrenalectomy. Histopathology identified a 7.5cm adrenocortical carcinoma with fat and vascular invasion, a modified Weiss Criteria score of 6, and a Ki67 index of 15-20%.

Post operatively blood pressure improved to 130mmHg on two agents and potassium normalized off Spironolactone. Cortisol, testosterone and DHEAS levels declined precipitously in keeping with suppression of the contralateral adrenal gland. She was commenced on Mitotane therapy given the high-risk features of adrenocortical carcinoma.

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How often can we make a pre-operative diagnosis of Gastroenteropancreatic NET? Single surgeon series

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Aim: To review the single surgeon experience of histologically proven GEP-NET with a view to analyse the data to answer the question -how often a pre-operative diagnosis is possible?

Materials/Methods: Reviewed the cases diagnosed as Neuroendocrine tumors from the logbooks, power point presentations and personal memory of last 12 years. There were 10 cases and analysed with regards to presenting symptoms, investigations, pre-op diagnosis established or not, surgery done or not and final histological diagnosis.

Results: Two cases of insulinoma diagnosed pre-op but only one was localised pre-op and confirmed even after exploratory surgery. Carcinoid tumors were diagnosed twice, one was localised pre-op. Three cases of primary liver carcinoid all of which are diagnosed post resection. One with multiple liver mets with no localisation of primary. One periampullary tumor diagnosed as Neuroendocrine carcinoma post pancreaticoduodenectomy though suspected pre-op. One pancreatic neuroendocrine carcinoma in a very young female who presented as Hemorrhagic Entericus.

Conclusions: Only two out of ten (20%) neuroendocrine tumors were diagnosed pre-op. Delay in diagnosis remains the characteristic feature of NET due to vague initial symptomatology. Despite the advances in imaging in general, there is paucity of investigation in neuroendocrine tumor disease. There is lack of molecular prognostic factors to identify high risk patients.

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Hemosuccus Entericus Is It NET?

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Introduction. Neuroendocrine tumors have variable presentation. Hemosuccus entericus (HE) as a clinical sign is rare and NET presenting as bleeding through papilla is a remote possibility.

Materials : 22 yrs female otherwise fit and healthy with dyspeptic symptoms of 12 months duration, presented to the gastroenterologist with upper abdominal pain with anemia. An OGD revealed blood oozing from the papilla -Hemosuccus Entericus. Contrast enhanced CT revealed a cystic lesion in the tail of pancreas compressing the splenic vein causing sectoral portal hypertension. An angiogram was done and attempted embolisation for what it thought to be Splenic Artery Pseudoaneurysm. Though hemo-dynamically stable, there was slow drop in Hemoglobin. Laparotomy done and distal pancreatectomy with spleen performed. Post operative recovery was uneventful.

Result: Nodular mass 5.5x 4 x 3.5 cm , grey white to grey brown. Tumor cells arranged in nests and papillary pattern with mitotic figures 0-1/HPF. Nuclear grade 2.

Conclusion: The final diagnosis is Pancreatic Neuroendocrine carcinoma with capsular infiltration

Atypical presentation of ectopic ACTH/gastrin secretion in an atypical lung carcinoid patient

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A 71 y.o. ex-smoker presented with several months of nausea, anorexia, weight loss, vague upper abdominal discomfort. Subsequent investigations diagnosed FDG-PET avid atypical lung carcinoid with hepatic metastasis. Ga-68-Dototate PET scan revealed low-grade somatostatin receptor expression in the left upper lobe with left suprahilar mass only. He underwent systemic chemotherapy with capecitabine, temozolamide. Following completion of chemotherapy and cessation of dexamethasone, he was noted to 10kg weight gain with moon-like facies, hyperglycemia, bilateral pitting oedema. Re-staging FDG-PET imaging revealed partial metabolic response. Blood pressure was 150/80mmHg despite increase of felodipine dose.

Serum cortisol was elevated at 1034nmol/L (range 110-550nmol/L) with an ACTH of 97pg/ml (range <46pg/ml), potassium was 2.9 mmol/L. MRI pituitary did not identify any pituitary lesion. Low and high dose dexamethasone suppression tests suggested ectopic ACTH secretion. Adrenal enzyme blockade with metyrapone was commenced with addition of ketoconazole. There was initial concern of persistent hypercortisolism (>800 nmol/L) despite up-titration of therapy, however this was due to the cross-reactivity of upstream adrenal metabolites due to enzyme blockers. Subsequent serum cortisol levels performed on liquid chromatography-tandem mass spectrometry (LC-MS) was at target (300 nmol/L).

Since his cortisol, potassium, blood pressure and glucose were controlled on dual adrenal enzyme blockade, and FDG-PET was stable, further systemic therapy was not given. However he developed profuse secretory diarrhoea with mildly elevated 24 hr urine 5-HIAA and elevated gastrin (305 pmol/L, range 6-55) with normal endoscopies. Diarrhoea resolved after commencement of somatostatin analogue injection. He is awaiting repeat Ga-68-Dototate PET to assess suitability for peptide receptor radionuclide therapy given his ectopic ACTH/gastrin secretory neuroendocrine tumour.

Ectopic Acromegaly due to GHRH-secreting Bronchial Tumour

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Case presentation:

A 59-year-old ex-smoker presented with abdominal pain and constipation. Acromegalic features were noted, with history revealing facial coarsening and acral enlargement over a 5-year period. His growth hormone failed to suppress after 75g oral glucose and his IGF-1 level was six times the upper limit of normal. An MRI revealed pituitary enlargement. X-rays and CT chest revealed a 5x7x6cm left perihilar mass. FDG PET/CT demonstrated FDG avidity in the perihilar mass, pituitary and right lower thyroid pole. Ga-68 DOTATATE PET/CT demonstrated somatostatin receptor activity within the lung mass and the pituitary. Thyroid ultrasound revealed a multinodular goitre, with a benign aspiration result from the dominant nodule.

The patient underwent a left pneumonectomy, with histology confirming a Growth Hormone Releasing Hormone (GHRH) secreting carcinoid tumour; 0/18 lymph nodes were involved. Postoperatively, acromegalic features improved, serum GHRH was normal and MRI showed a reduction in pituitary size, however, GH and IGF-1 remained elevated. Repeat CT chest revealed an enhancing left thoracic cavity soft tissue lesion. The patient is being assessed for recurrent carcinoid and the development of a somatotrophinoma. Genetic testing for Multiple Endocrine Neoplasia 1 and 4 was negative.

Discussion:

Ectopic GHRH secretion is responsible for <1% of cases of acromegaly [1]. The majority of these cases are due to bronchial carcinoid tumours and pancreatic neuroendocrine tumours, which are both associated with MEN-1[1-3]. Pituitary hyperplasia resulting from GHRH hypersecretion develops in up to 60% of cases and may be indistinguishable from an adenoma [1]. Suspicion for ectopic acromegaly arises when there is discordance between features of acromegaly and MRI pituitary. Plasma GHRH determination is useful as elevated levels have been found in all cases of ectopic GHRH-secreting tumours, but not found in patients with somatotroph adenomas (2,4). Complete tumour resection is the only curative treatment for ectopic acromegaly.

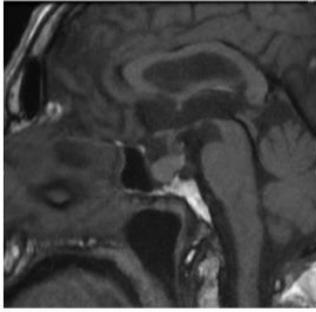


Figure 1a:
Preoperative MRI showing pituitary enlargement.

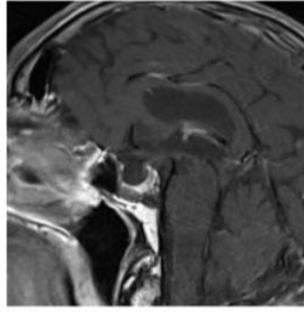


Figure 1b:
Postoperative MRI showing reduction in pituitary size

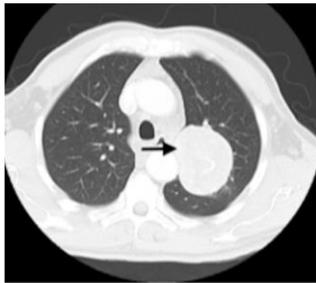


Figure 2:
CT chest demonstrating a 5 x 7 x 6 cm left perihilar mass.

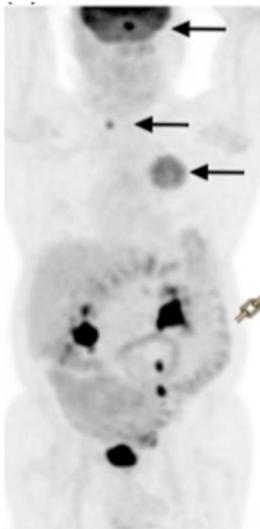


Figure 3:
FDG PET/CT scan showing FDG avidity in the left perihilar mass, pituitary and right lower thyroid pole.

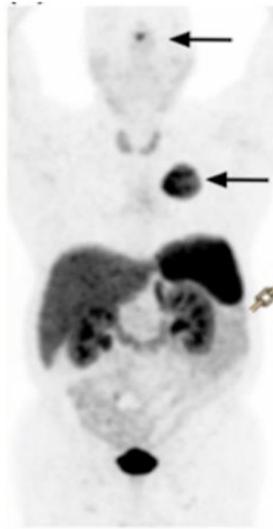


Figure 4:
Ga-68 Dotatate PET/CT scan showing somatostatin receptor activity within the lung mass and pituitary.

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A case highlighting the value of ⁶⁸Ga-dotatate PET/CT in the diagnostic dilemma of post-prandial hyperinsulinaemic hypoglycaemia.

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A 63 year old man presented with symptomatic post-prandial hypoglycaemia following fundoplication for gastro-oesophageal reflux. A mixed meal test provoked post-prandial hyperinsulinaemic hypoglycaemia (BGL 1.9mmol/L, insulin 21.4 U/L, C-peptide 2280pmol/L). Differential diagnoses included non-insulinoma pancreatogenous hypoglycaemia syndrome, "dumping" syndrome and less likely insulinoma. A gastric emptying study did not demonstrate "dumping" and prolonged fast did not provoke fasting hypoglycaemia. Surprisingly ⁶⁸Ga-dotatate PET/CT identified focal somatostatin activity in the pancreas consistent with an insulinoma.

Laparoscopic distal pancreatectomy was performed however histology demonstrated normal pancreatic tissue. Post-operatively the patient developed recurrence of symptoms. Repeat ⁶⁸Ga-dotatate PET/CT demonstrated an unresected insulinoma abutting the resection margin. An open distal pancreatectomy was performed. Histopathology confirming a pancreatic endocrine tumour with no features of nesidioblastosis. There was no further recurrence of the patient's symptoms.

Insulinomas are rare gastroenteropancreatic neuroendocrine tumours, the majority (>90%) are solitary, intrapancreatic and benign.^{1,2} Surgical resection is required for cure however pre-operative localisation is limited by their small size (90% are <2cm).² The sensitivity of abdominal CT to localize insulinomas is 64%, MRI 75%, endoscopic ultrasound 65% and intra-arterial calcium stimulation testing 63%.³ Somatostatin receptor type 2 expression is present in 69% and GLP-1 receptors almost universally expressed in insulinoma thus imaging with ⁶⁸Ga-dotatate PET/CT and ⁶⁸Ga-exendin-4 PET/CT frequently localizes insulinoma not identified by conventional imaging.^{4,5,6}

Patients with insulinoma typically present with fasting hypoglycaemia with the diagnosis involving biochemical demonstration of endogenous hyperinsulinaemic hypoglycaemia. Very rarely a mixed meal test will demonstrate post-prandial hypoglycaemia in patients with insulinoma as reported in a Mayo series (1987–2007) where only 6% of patients with insulinoma presented with post-prandial hypoglycaemia and only 3 of these demonstrated a negative 72 hour fast.⁷ This case highlights the accuracy of nuclear medicine functional imaging and its value in the diagnostic paradigm in patients presenting with hyperinsulinaemic hypoglycaemia.

Impact of [68Ga]-DOTATATE PET after resection of appendiceal NEN: A retrospective study

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Aims: Neuroendocrine neoplasms are a heterogeneous group of tumours which are increasing in incidence. Appendiceal NENs are often incidentally detected, are generally benign and carry a low risk of recurrence. (Singh 2018) [68Ga]-DOTATATE PET is known to be more sensitive than cross-sectional imaging, and is increasingly used in postoperative imaging to ensure there is no residual disease. We hypothesize that these scans have a low likelihood of showing residual disease in patients with low-risk appendiceal NENs (appNENs).

Methods: Retrospective study of all patients who underwent [68Ga]-DOTATATE PET at Royal North Shore Hospital 0-18 months after resection of appendiceal NEN. Scans were reviewed independently of original report by an experienced nuclear medicine physician. The primary outcome was the proportion of patients whose scans demonstrated PET uptake to suggest residual disease.

Results: From 2011 to 2014 25 consecutive patients were identified in the pilot phase of the study. The median age was 32 (range 17-74) and 64% were female. The median time after surgery was 4.3 months (range 0.3-17.6). All patients underwent appendiceal resection and three subsequently underwent hemicolectomy due to high-risk pathology. Pathology was as follows: Size - median 9mm (range 1-32). Location – distal 73%, middle 20%, proximal 7%. All tumours were well-differentiated and Grade 1 where graded by WHO 2010. No scans showed definitive residual or distant disease. 3/25 scans showed abnormalities requiring follow-up – one unrelated to neuroendocrine pathology (thyroid uptake) and two indeterminate (bowel loop, vertebral lesion).

Conclusions: Post-operative use of [68Ga]-DOTATATE PET did not detect any residual or distant disease after resection of appNENs. Despite its superior sensitivity compared to cross-sectional imaging, it is not recommended as part of staging after completely resected localized appNENs.

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Renal function influences renal absorbed dosimetry, haematologic toxicity and early withdrawal from ¹⁷⁷Lu-DOTATATE treatment

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BACKGROUND:

Peptide receptor radionuclide therapy (PRRT) is a safe and highly effective treatment for advanced neuroendocrine tumours (NET). Treatment is usually administered using fixed administered activity (7.4GBq) protocol without considering predictors of dose limiting toxicities to organs-at-risk. Our study examines the relationship between renal function and renal-absorbed-dosimetry (RAD) as predictors of haematologic toxicity.

METHODS:

Retrospective audit of patients with advanced NET treated with induction ¹⁷⁷Lu-DOTATATE at Royal Brisbane and Women's Hospital between September 2014 to August 2017. Renal function as measured by isotopic renal glomerular filtration rate (iGFR) was correlated with multiple timepoint RAD for first treatment cycle, and change in haematologic parameters (haemoglobin, white cell count, neutrophils, leukocytes, platelets) at baseline, nadir and last follow-up (<6 months after final treatment cycle). Toxicity was graded from 0 to 5 according to CTCAE v5.0 of the NCI.

RESULTS:

We analysed 61 patients with a mean age 66 (range 30-91) and predominantly small bowel (43%) and pancreatic (39%) NET. Patients received 1-4 cycles of PRRT at 8-week intervals with median cumulative administered activity of 33GBq. There was moderate negative correlation between cycle 1 RAD and baseline iGFR (-0.42). There was significantly higher RAD in patients who received <4 cycles LuTate (vs 4 cycles; 8.1Gy vs 6.2Gy, p=0.031) and grade 2-4 anaemia (vs grade 0-1; 9.1Gy vs 5.84Gy, p=0.004). These patients also had significantly lower baseline iGFR (<4 cycles LuTate, 66 vs 82ml/min/1.73sqm, p=0.005; and grade 2-4 anaemia, 64 vs 84ml/min/1.73sqm, p=0.001). There was no significant difference between cycle 1 RAD or baseline iGFR for other measured parameters of haematologic toxicity.

CONCLUSION:

There is moderate negative correlation between iGFR and RAD during induction PRRT. Patients with higher RAD or lower baseline iGFR are more likely to experience grade 2-4 anaemia or fail to complete 4 planned induction cycles due to myelosuppression.

Comparability of ⁶⁷Cu-SARTATE and ¹⁷⁷Lu-DOTA-octreotate efficacy in a preclinical model of neuroendocrine tumour

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PRRT using radiolabelled octreotate is an effective treatment for SSTR2-expressing NETs. Given the diagnostic and therapeutic potential of the copper isotopes, Cu-64 and Cu-67, respectively, we are developing a novel SSTR2 targeting conjugate as a theranostic agent. ⁶⁴Cu-SARTATE has been successfully trialled as an imaging agent and potential prospective dosimetry tool in NET patients. As the therapeutic effects of this agent are yet to be determined, the aim of this study was to explore the efficacy of ⁶⁷Cu-SARTATE in a preclinical model of NET and compare it with that of ¹⁷⁷Lu-DOTA-octreotate (¹⁷⁷Lutate).

Mice bearing AR42J xenografts were randomized into treatment groups to receive saline, ¹⁷⁷Lutate or ⁶⁷Cu-SARTATE via intravenous injection. Tumour volumes were measured twice weekly and percentage tumour growth inhibition (TGI) was calculated. Kaplan Meier survival curves were analysed using the Mantel Cox log rank test.

All treatments were well tolerated. Dose dependent TGI was observed after single administrations of ⁶⁷Cu-SARTATE and ¹⁷⁷Lutate. Survival was extended from 12 days in the control group to 21 and 26 days following 5 and 20 MBq ⁶⁷Cu-SARTATE, and 21 and 29 days following 5 and 25 MBq ¹⁷⁷Lutate. In a second study, the efficacy of fractionated delivery of PRRT was assessed. Administration of a total of 30 MBq ⁶⁷Cu-SARTATE or ¹⁷⁷Lutate as two 15 MBq fractions two weeks apart improved survival compared with that when delivered as a single fraction (⁶⁷Cu-SARTATE: 47 vs 33 days; ¹⁷⁷Lutate: 46 vs 29 days). Furthermore, the efficacy of ⁶⁷Cu-SARTATE and ¹⁷⁷Lutate was equivalent on both treatment schedules.

In conclusion, fractionated administration of ⁶⁷Cu-SARTATE and ¹⁷⁷Lutate was more efficacious than a single fraction. The efficacy of ⁶⁷Cu-SARTATE in the AR42J tumour model was equivalent to that of ¹⁷⁷Lutate, demonstrating the suitability of this novel agent for clinical assessment in the treatment of SSTR2 expressing NETs.

Neuroendocrine neoplasms in the paediatric adolescent and young adult population in New Zealand and Queensland Australia

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BACKGROUND: Multiple studies have shown the incidence of Neuroendocrine neoplasms (NENs) to be increasing worldwide. However, information in the paediatric, adolescent and young adult (PAYA) patient group is sparse globally. This retrospective population-based analysis describes the incidence and mortality of NENs in the PAYA population in two regions with similar population sizes - New Zealand and Queensland, Australia.

METHODS: Data regarding individuals <30 years diagnosed with NENs between 2008 and 2012 was obtained from the Queensland Oncology Repository and the New Zealand based NETWORK! Register. Findings include overall and site-specific incidence, histopathologic subtype, and cause specific mortality.

RESULTS: 170 NENs were diagnosed in Qld and 123 in NZ between 2008 and 2012. 65% in NZ and 68% in Qld were females. The majority (>84%) in both populations occurred in patients 15 years of age and above. 79% of all NENs in Qld and 68% in NZ were in the appendix. 3 (1.7%) of the Qld and 9 (7.3%) of the NZ PAYA cohort had died of NEN.

In the subgroup <15 years 27 NENs were identified in Qld and 16 in NZ. The majority (>87%) occurred in the age group of 10 years and above in both cohorts. 25 Qld and 8 NZ cases were located in the appendix. 2 deaths were identified in the NZ cohort and no death occurred in Qld.

CONCLUSION: This study represents a comparison of two regions with similar population sizes and shows that the presentation of NENs in these two populations were found to be similar, with the majority of NENs in the PAYA population occurring in the appendix. Further work is required to understand subtle differences between the two data sets, which will provide important context to understanding other world comparisons of NEN epidemiology.

Staged IVC venous sampling for ACTH in a Von-Hippel-Lindau syndrome (VHL) patient with Cushing's syndrome, pancreatic neuroendocrine tumor and renal cell carcinoma

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Introduction

Outlining the source of ACTH in a VHL patient with Cushing's syndrome can be quite challenging as the origin of the hormone could either come from the pancreatic neuroendocrine tumor (NET) or the renal cell carcinoma (RCC).

Case description

A 31-year-old lady with type 2 diabetes, who was in her second trimester of third pregnancy, experienced rapid weight gain and accelerated hypertension. She had florid features of Cushing's syndrome with a family history of VHL. Initial laboratory results revealed potassium of 2.5 mmol/L, bicarbonate 30 mmol/L and morning cortisol of 2823 nmol/L. Her serial 24-hour urine cortisol ranged from 1122-14710 nmol/L together with elevated ACTH level (18.8 pg/ml) and serum Chromogranin A (530.2 ng/mL). Repeated urine catecholamines were otherwise normal. She had caesarean section at 28 weeks gestation due to placental insufficiency. Post-delivery hypercortisol state was controlled by oral Ketoconazole 400mg TDS and oral Metyrapone 250mg TDS. MRI Pituitary did not show any discernible pituitary lesion. CT abdomen revealed complete replacement of the pancreas by mixed solid and cystic lesions measuring 2.5 to 4.0cm. There was also solid mass seen in the midpole of right kidney measuring 3.7 x 2.5 x 4.0 cm. A super selective sampling of the IVC for ACTH together with bilateral inferior petrosal sinus sampling was performed to delineate the source of ACTH. ACTH level arising from the hepatic vein that was corresponding to the pancreatic drainage was higher than the rest. Total pancreatectomy and right nephrectomy were done. The histopathological examination revealed mixed-serous pancreatic NET with RCC. Glucocorticoid replacement and Creon were commenced after surgery.

Conclusion

In a VHL patient with Cushing's syndrome and the presence of both pancreatic NET and RCC, a selective venous sampling of IVC is an important work up to delineate the source of ACTH.

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