# Selected updates from ENETS 2017

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# Summary

- ENETS 2017 was an invigorating and stimulating meeting of the world leaders in the management of neuroendocrine cancers
- Of special significance this year was the in inclusion of a ‘Patient-focused’ stream at which our CEO, Simone Leyden presented a lecture focused on the unmet needs of neuroendocrine cancer patients
- ENETs remains the pre-eminent meeting for neuroendocrine cancers worldwide and Australia investigators and Doctors are well regarded at this meeting.

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# A. Basic Science – Signaling pathways, receptors, biomarkers

- *Lelek S et al*, **Antiproliferative Effects of Lanreotide in NETs**
  - Neuroendocrine tumours of the lung (bronchopulmonary) are classified as typical or atypical and have a varied behaviour of growth. The anti-tumour effects of octreotide such as lanreotide is proven in gastroenteropancreatic (GEPNETS) but its use for lung NETs is less defined
  - In this preclinical study, typical and atypical lung NET cells were treated by a protocol of lanreotide or lanreotide in combination with PI3K alpha inhibitor (BLY719).
  - The results reveal that lanreotide did inhibit tumour growth in both atypical and typical lung NETs but there was a better effect with the combination of BLY719

  Conclusion
  - Lanreotide treatment is promising in lung NETs and may be enhanced by combinations with other targeted therapies.

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# B. Basic Science – Genetics, Epigenetics

- *Fatima A et al.* **Development of Neuroendocrine Tumours in Patients with a family history of NET or any other cancer**
  - Very little is known about the risk factors for NET, however we know that they can arise in hereditary syndromes eg MEN, Von Hippel Lindau, Neurofibromatosis etc
  - More than 500 patients with NET were identified and matched with controls
  - A significant relationship was seen between first degree relatives with cancers and the development of NETs especially in the pancreas, lung, stomach and small intestine

  The study concluded that first degree relatives with any diagnosed cancer or particularly NET is a risk factor for NETs.

# D. Epidemiology/natural history/prognosis – registries and surveys

- *Basuroy R et al.* **Incidence and characteristics of ileocolonic NET identified in the UK Bowel Cancer Screening Program**
  - This study aimed to identify the number of NETs diagnosed through the United Kingdoms bowel cancer screening program
  - During the period of 2006-2014,216,707 patients had colonoscopies, of which 146 patients had NET codes:
  - 102 (70%) Colorectal; 24 (16%) terminal ileum;18 (12%) unknown; 2 (1%) appendix.
  - The incidence of ileo-colonic NETs was 67 per 100,000 colonoscopies per year of which 24% had metastatic disease.

  This study is the first to report on the incidence of large bowel NETs in a screening program (UKBCSP) and also revealed that the rates of metastases was lower than previous studies and may be indicative of the positives of screening colonoscopies in this group

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- *Ovcinnikova O et al.* **Epidemiology of Carcinoid Heart Disease (CHD) in Patients with Carcinoid Syndrome (CS): A Systematic Literature Review**
  - Carcinoid heart disease develops in the context of carcinoid syndrome due to the exposure and overproduction of serotonin (a vasoactive hormone)
  - Perioperative mortality from open heart valve surgery remains 10-20% but is lower in experienced centres and when patients recover from their surgery better functional outcomes were achieved (ie better overall health)
  - From this literature review, it was revealed that over the past decades, improved management of carcinoid syndrome (with octreotide) and carcinoid heart disease (earlier surgery) has increased patient survival. Also the number of patients progressing onto having carcinoid heart disease is in the order of 15-30% rather than previous estimates of 20-70%

- *Westin G et al.* **Pancreatic Neuroendocrine Tumours (pNETs): A population-based Analysis of Epidemiology and Outcomes.**
  - pNETs are rare neuroendocrine cancers, however the incidence and stage at diagnosis is changing.
  - The SEER Registry was analysed between 200-2013 with 5993 pNET patients studied.
  - During the time annual incidence has increased from 0.3 to 1.2/100,000 (4 fold increase), the majority of this increase was in patients diagnosed ‘incidentally’ with localised tumours to the pancreas
  - Overall survival for patients with pNETs has improved significantly since 2008 and factors that were favourable for longer survival were – younger age, female sex, early stage of disease, low grade and surgery (even in metastatic disease)
  - 5 year survival for local disease was 82%; locally advanced disease 65% and widespread metastatic disease (at diagnosis) 26%

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- *Wyld D et al.* **Neuroendocrine Neoplasm trends over 32 years in Queensland, Australia (Selected for an oral presentation)**
  - This was a retrospective analysis of the number of patients diagnosed or coded for neuroendocrine cancer in the Queensland Oncology Repository
  - Between 1982 and 2014, 3,696 patients were diagnosis with NET. Median age at diagnosis was 60, 49% were male and 35% were from rural Queensland.
  - The incidence of NETs increased over the time from 1.4 cases to 6.7 cases per 100,000
  - Over the last 5 years NETs of the small bowel have become the most common site.
  - Improved 5 year survival was shown over the same period – 78% to 93%.

- David Wyld is a NET specialist oncologist at Royal Brisbane Hospital, Queensland

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- *Cavalcoli F et al.* **High rate of second neoplasms in patients with a bronchial (lung) tumour**
  - Lung NETs are classified as typical carcinoids, atypical carcinoids, large cell neuroendocrine carcinomas or small cell lung carcinomas
  - 47 patients with lung NETs were analysed between 1995 – 2015, patients with small cell lung carcinomas were excluded.
  - 44 patients underwent surgery, 5 developed metastatic disease.
  - 14 patients have been diagnosed with a second type of cancer, the most common type was squamous cell lung cancer, colorectal cancer and kidney cancer.
  - This study observed a high rate (14/47) of secondary cancers being diagnosed which suggests that all patients with lung NETs should be carefully followed and monitored.

- *Massironi S et al.* **A role for Vitamin D in the gastroenteropancreatic neuroendocrine neoplasms outcome: Report on a series from a single institute**
  - Vitamin D deficiency is hypothesised to be an independent risk factor in the development of a number of cancers
  - This study looked at Vitamin D deficiency in NET patients and assessed the association with overall survival and progression of the disease
  - Between 2010 – 2015, 138 patients with GEP NETs were enrolled.
  - 68% of patients had clinically low levels of vitamin D
  - The results showed that there was an ‘association’ between low vitamin D and overall survival and the researchers concluded that vitamin D supplementation may influence clinical outcome

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- *Massironi S et al.* **Effects of low doses of aspirin on clinical outcome and disease progression in patients with Gastroenteropancreatic neuroendocrine (GEPNET) tumours: Results from a multicentre retrospective study**
  - The preventative effect of aspirin on the development of colorectal cancer has been observed, however, the impact on GEPNETs has not been evaluated
  - All the GEPNET patients in 3 European Centres were retrospectively enrolled between 2005-2016. The relationship between aspirin use and disease grading, stage, primary site and overall survival were made.
  - 253 patients were included with primary sites being stomach, pancreas, small bowel, colon and appendix and unknown
  - There was no clear survival benefit in those patients taking aspirin, however, taking aspirin was associated with lower Ki-67 values and less lymph node involvement, but more study into aspirin's effect is needed

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# F. Epidemiology/natural history – descriptive epidemiology

- *Demetriou G et al.* **Clinical outcomes in small neuroendocrine tumours treated with intestinal surgery in tertiary centre.**
  - Patients with small bowel NETs may require surgery to remove them either as an emergency or electively
  - 37 patients underwent small bowel surgery in the hospital, their data was analysed retrospectively
  - Of the 37 patients – 86% had symptoms; 70% had liver metastases; 81%had lymph nodes and/or scarring and changes in the mesentery (desmoplasis)
  - The results showed that patients who had surgery had significant symptom resolution and improvement

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- *Santos AP et al.* **Abdominal obesity, fasting glucose and metabolic syndrome are risk factors for well differentiated digestive neuroendocrine tumours**
  - Gastrointestinal NETs are increasing. Increased obesity and metabolic syndrome (high insulin levels and abnormal cholesterol) is associated with the development of many cancers.
  - This study looked at 96 gastrointestinal NET patients and matched them with case control patients
  - From this study it was found that waist circumference (>80cm in women; >96cm in men); high triglyceride levels; high fasting glucose levels and metabolic syndrome were risk factors for gastrointestinal NETs and was significantly higher if patients had more than 4 risk factors.

# H. Biomarkers

- *Hayes AR et al.* **Peripheral blood biomarkers of systemic inflammation may be prognostic in metastatic gastroenteropancreatic NET patients following Lutate.**
  - Neutrophil-to-lymphocyte ratio (NLR) and lymphocyte to monocyte ratio (LMR) (white blood cells) is used as a prognostic marker in certain solid tumours but its value in well differentiated NETs is less defined.
  - 84 patients who received lutate for symptom control or progressive disease were analysed and compared the NLR, LMR to histological grade and progression free survival
  - LMR and LMR have potential prognostic biomarkers in patients with advanced GEPNETs and are worthwhile investigating further

- This trial was performed by the team at Sydney Vital, Royal North Shore Hospital and St George Hospital.

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# K. Medical Treatment – somatostatin analogues and interferon

- *Chan D et al.* **Escalated dose somatostatin analogues for anti-proliferative effect in gastroenteropancreatic (GEPNETS) neuroendocrine tumours: A Systematic review**
  - Somatostatin analogues (lanreotide, sandostatin) are the cornerstone of treatment for well-differentiated GEPNETs. Increase the dose of somatostatin in trialed in patients to maximise effect but small studies have revealed mixed results
  - 19 studies were identified for analysis.
  - The results revealed symptom improvement 23-100% and biochemical improvement 27-100% with disease control rate being high but objective response rate (ie tumour shrinkage) was modest. The most common side effects of dose escalation were fatigue, diarrhoea, abdominal pain, and gall stones
  - There is a need for large prospective studies investigating the role of dose escalation with somatostatin analogues

- *Elgendy K et al.* **Perioperative carcinoid crisis during surgery – who benefits form octreotide?**
  - Cardiovascular instability as a result of carcinoid crisis is poorly understood but can be seen in patients with gastrointestinal NETs during surgery
  - In this centre they used an infusion of octreotide pre surgery for 24 hours as a protocol, but 77% of patients had preoperative octreotide for more than 4 hours.
  - The analysis of the 54 patients revealed that octreotide infusion reduces the incidence and severity of the cardiovascular instability during surgery but it was not universal with almost all patients undergoing bowel or liver surgery in the presence of liver metastases having some instability during the procedure.

- *Pavel M et al.* **Safety and efficacy of 14 day dosing interval of lanreotide for patients with pancreatic or midgut neuroendocrine tumours progressing on lanreotide every 28 days: The prospective, open label, international, phase 2 CLARINET FORTE study**
  - CLARINET demonstrated the antitumour effect of lanreotide 120mg every 28 days fo metastatic gastroenteropancreatic NETs
  - In this study the dosage remained the same but was given every 2 weeks (14 days)
  - Selection criteria: Well differentiated, metastatic/locally advanced, unresectable, functioning/non-functioning, G1/G2, pancreatic or midgut NETs

- This study is recruiting and the UF will find out if there are sites in Australia for patients to be recruited at.

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- *Pavel M et al.* **Telotristat Ethyl in carcinoid syndrome: safety and efficacy results of an open-label extension of the TELCAST phase 2 clinical trial.**
  - Telotristat is a tryptohan hydroxylase inhibitor which blocks the final step in the production of serotonin in the body. It is marketed as Xermelo.
  - It is used in addition to a somatostatin analogue to help treat the symptoms of carcinoid syndrome – flushing, diarrhoea, palpitations, wheezing, carcinoid heart disease
  - This study showed that telotristat was well tolerated and that it reduced the frequency of diarrhoea and other carcinoid symptoms and also reduced the levels of urinary 5-HIAA (a breakdown product of serotonin) over a 48 week period

# M. Medical treatment - others

- *De Hosson LD et al.* **Towards optimal personalised diet and vitamin supplementation in NET patients; A Feasability Study.**
  - Patients with NETs often have gastrointestinal complaints due to the somatostatin analogues, tumour secretion of hormones. This can lead to impaired absorption of critical minerals and vitamins. Patients with carcinoid syndrome may also have low tryptophan (an ingredient in serotonin).
  - The results showed that NET patients are at risk of vitamin deficiencies and there is a need for personalised dietary advice and multivitamin supplementation

# N. PRRT – Ablative therapies – endoscopy - surgery

- *Brabander T et al.* **Pitfalls in the response evaluation after PRRT with lutate.**
  - PRRT with lutate is a treatment with good results in patients with metastatic GEPNETs
  - The aims of this study were to identify the pitfalls that should be taken into consideration when monitoring response after PRRT
  - 354 Dutch patients were enrolled and treated between 2004-2011.
  - Liver function tests and Chromogranin A were measured before and after treatment
  - Results showed an increase in liver function tests in 25% compared to baseline in both those who showed an objective response (shrinkage) or stable disease
  - Chromogranin A increased in 30% after PRRT in patients with an objective response or stable disease and 34% in patients with progressive disease. In 70% of patients, chromogranin A returned to baseline after therapy.
  - Clinicians should be aware that biochemical changes during testing following PRRT are common and may occur due to radiation induced inflammation or disease progression and that repeated measures are necessary to differentiate between the two.

- *Kong G et al.* **Peptide receptor radionuclide therapy (PRRT) for treatment of functional and metastatic Phaeochromocytoma (PCC) and Paraganglioma (PGL).**
  - Treatment options for metastatic PCC and PGL and related hypertension (high blood pressure) are limited
  - Experience with PRRT suggests good disease control but uncertain effects on blood pressure control
  - 16 patients across 2 centres enrolled.
  - Results 6/12 patients had high blood pressure control with reduction in medications at 3 months post PRRT; 5 had blood pressure stabilsation. 90% had reduction in Chromogranin A
  - 40% of patients had disease regression on CT scan and stable findings in another 40%.
  - One patient experienced significant drop in white cell count.
  - PRRT showed favourable disease control with minimal toxicity but warrants further trials

- Peter MacCallum was a site for this study and lead author is Dr Grace Kong

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- *Smit Duijzentkunst D, Kwekkeboom D.* **Treatment of Paragangliomas with Lu-177 Octreotate based PRRT**
  - Paragangliomas are a diverse/heterogeneous group of tumours that can express somatostatin receptors on the cells that can be targeted by radiolabelled peptides
  - 11 patients with extra-adrenal and 17 patients with head and neck paragangliomas received a total of 104 doses of PRRT
  - An objective response was seen in 36% of patients and mean progression free survival was 30 months.
  - This study concluded that PRRT was a safe and effective treatment for inoperable or metastatic paraganglioma and should be included in the treatment algorithm for the disease.

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# O. Surgery

- *Kaemmerer D et al.* **Primary tumour resection results in superior overall survival after PRRT in advanced neuroendocrine neoplasms**
  - It is still unclear whether resection of the primary NET improves overall survival after receiving PRRT
  - 1048 patients were retrospectively analysed, all had advanced NET disease and had received PRRT. In 541/1045 (52%)patients, the primary tumour was removed; 444 (42%) had no resection and no data was found on 66 (6%) patients.
  - 37% of patients had their primary tumour removed from the pancreas, and 30% had it resected from the small bowel
  - The results indicated that patients who had surgery of their primary tumours had a better overall survival and progression free survival after PRRT and it is recommended that wherever feasible the primary tumour should be removed

# Q. Case Studies

- *Stavrides-Eid M et al.* **Immunotherapy in a Young Adult with Atypical neuroendocrine tumour**
  - Use of immune therapy PD-1 antibody is emerging as a treatment option for solid tumours. In the setting of NETs little is known for this. Current studies are underway looking at immune therapy in high grade NETs but the outcomes are not known.
  - Pembrolizumab (keytruda) was used in a 39 year old patient with advanced thymic carcinoid tumour that had surgery, chemotherapy, sunitinib and lanreotide. His chief complaint was shortness of breath due to the size of the tumour in his chest (mediastinum).
  - The patient had 5 cycles of pembrolizumab (keytruda) and showed radiological and biochemical improvement with shrinkage in the tumour and improved symptoms
  - Further trials of immunotherapy in NETs are needed