Australian Neuroendocrine Tumours (NETs) Consensus Workshop Report

Meeting Management Challenges in Australia.

July 2008

Australian Neuroendocrine Tumours (NETs) Consensus Workshop

Meeting Management Challenges in Australia

Clinical Oncological Society of Australia (COSA)

Australian and New Zealand Hepatic, Pancreatic & Biliary Association (ANZHPBA)

Australasian Gastro-Intestinal Trials Group (AGITG)

Australian and New Zealand Society of Nuclear Medicine (ANZSNM)

Hilton Hotel, Melbourne Airport, 28 July 2008

Summary report

Workshop report prepared by Alison Evans Consulting on behalf of COSA

September 2008

Workshop supported by unrestricted educational grants from Ipsen Pty Ltd, Novartis Pharmaceuticals Australia, SIRTeX Medical and the ANZHPBA

BACKGROUND

Neuroendocrine tumours (NETs) are a rare group of heterogeneous neoplasms arising from the diffuse neuroendocrine system of the gastrointestinal tract or bronchopulmonary system. The annual incidence of gastroenteropancreatic NETs (GEP-NETs) has been estimated at 2.5–5 cases per 100,000.[1] Australian cancer registry-derived data for the period 2000–2004 suggest an annual incidence of around 3.3 cases per 100,000.[2] This is likely to be an underestimate given that only tumours considered to be malignant are reported to registries.

GEP-NETs present a unique set of issues in relation to both diagnosis and management. Some may secrete neuropeptides, causing a range of clinical syndromes, including the carcinoid syndrome. Nevertheless, many are clinically silent and in others, the non-specificity of the associated symptoms leads to delayed diagnosis. Consequently, many malignant tumours present only after metastasis has occurred.[3] Despite this, the clinical course of these diseases is varied; not infrequently patients have tumours that are indolent and progress slowly over several years. Specific treatment is not always required and symptoms related to the carcinoid syndrome or related hormonal manifestations of GEP-NETs can be controlled effectively using somatostatin analogues. Anti-tumour treatment is relatively ineffective and involves modalities such as surgery, liver directed therapy, radionuclide therapy or chemotherapy.

The heterogeneous and uncommon nature of GEP-NETs has resulted in limited high-level evidence on which to base recommendations for diagnosis and treatment. Despite these limitations, guidelines have been published in Europe and the USA. The European Neuroendocrine Tumour Society (ENETS) published consensus guidelines for the management of NETs of the stomach, duodenum and pancreas in 2006,[4] and for mid-gut and hind-gut tumours in 2008.[5] Consensus guidelines for the management of NETs were published by the US National Clinical Cancer Network (NCCN) in 2008.[6]

In Australia, the challenge of developing a standardised approach to the management of these rare tumours is compounded by limited access to many emerging investigations and treatments. Contributory factors include the country's diverse geography as well as lack of reimbursement. Professional bodies with an interest in the management of GEP-NETs in Australia include the Clinical Oncological Society of Australia (COSA), Australian and New Zealand Hepatic, Pancreatic & Biliary Association (ANZHPBA), Australasian Gastro-Intestinal Trials Group (AGITG) and Australian and New Zealand Society of Nuclear Medicine (ANZSNM). These groups, in collaboration with relevant industry groups, have identified a need for a strategic and collaborative approach to raising awareness in Australia of these rare and complex neoplasms, guiding best practice in their diagnosis and management and optimising service delivery.

WORKSHOP OVERVIEW

COSA, in collaboration with ANZHPBA, AGITG and ANZSNM, convened a 1-day workshop in Melbourne on 28 July 2008 with the aim of:

- understanding the consensus and controversies in the management of GEP-NETs across international guidelines and their implications for service implementation in Australia
- developing a minimum diagnostic set and a service model for Australian healthcare professionals involved in the management of GEP-NETs
- raising the profile of GEP-NETs amongst Australian clinicians.

The workshop program is provided as Appendix I.

The workshop, the first of its size to be held in Australia on this topic, was attended by over 80 participants from the specialties of medical oncology, nuclear medicine, surgery, radiology, endocrinology, gastroenterology, pathology and nursing as well as consumers and representatives from relevant cancer organisations (see Appendix II).

WORKSHOP INTRODUCTION

Professor David Goldstein, President of COSA, welcomed participants and emphasised the importance of a multidisciplinary and collaborative approach to planning and consensus regarding the management of GEP-NETs in Australia.

SUMMARY OF PRESENTATIONS

The workshop opened with a series of presentations providing context for the discussions that were held later in the day. A brief outline of the key points covered in each presentation is provided below.

NETs: the story so far

Professor Irvin Modlin *(Professor of Surgery, Yale University School of Medicine, Newhaven, USA)*

Professor Modlin gave an overview of the history of NETs, and outlined their natural history, pathology, biochemical investigation and diagnosis. He presented US data, including Surveillance Epidemiology and End Results (SEER) data, on the incidence of NETs, demonstrating:

- the high proportion of tumours that affect the digestive tract (predominantly the small intestine)
- the substantial increase in incidence of GEP-NETs over the past 3 decades compared with adenocarcinomas.

Based on these data and regression analysis, Professor Modlin predicted that the annual incidence of GEP-NETs over the next 3–4 years will be around 7.5–8 cases per 100,000 population.

Key points relating to the pathology and immunohistochemistry of GEP-NETs included:

- **pathology**:
    - paucity of current evidence on which to base decisions about prognosis and likelihood of distant metastases; this reflects the lack of both novel molecular markers and clarity in establishing the cellular origin and metastatic propensity of the tumours

    - lack of an accepted classification system for grading and staging of GEP-NETs (although validation of a staging and grading process for mid- and hind-gut NETs is underway by the ENETS)
- **immunohistochemical profiling**:
    - chromogranin A (CgA) and synaptophysin as key markers characterising the neuroendocrine origin of GEP-NETs
    - Ki-67 as the key marker of proliferative index, and the recognised association between increased mitotic rate and poorer outcomes
    - potential role of testing for secretory peptides specific to the tumour site and cells of origin
- **issues with current markers** that underscore the need for more sophisticated diagnostic technologies including:
    - risk of false positive results
    - inconsistent assays
    - relative insensitivity of assays
    - long turnaround time for test results
    - cost of testing (especially if used as a screening tool).

Professor Modlin described the potential for mathematical modelling to help identify genetic markers of tumour progression in GEP-NETs that could be used to determine prognosis prior to clinical evidence of metastasis.

As context for the workshop discussions, Professor Modlin summarised issues identified during a US National Cancer Institute summit held in 2007[7] to determine priorities for improving the management of GEP-NETs, including:

- paucity of investigators in GEP-NETs
- paucity of specific targets for new therapies
- shortage of *in vitro* and animal models to study disease pathogenesis and treatment
- lack of uniform pathological classification or staging system
- lack of molecular prognostic factors to identify high-risk patients and lack of understanding of the natural history of the tumours
- lack of centres offering the multidisciplinary expertise required for diagnosis, staging and management
- lack of understanding of the disease complications that lead to morbidity and mortality.

Suggested solutions identified to address these issues included:

- increased education about GEP-NETs
- increased funding for clinical and basic research
- conduct of large multicentre clinical trials of homogeneous patient groups
- consensus on classification regarding staging and grading
- development of minimal standards for diagnosis and classification
- development of databases
- development of multidisciplinary centres of excellence.

Conventional imaging in GEP-NETS

Dr Kate Moodie *(Radiologist and Nuclear Medicine Specialist, Peter MacCallum Cancer Centre, Vic)*

Dr Moodie provided an overview of the limitations of conventional imaging in the diagnosis and evaluation of NETs in the abdomen and pelvis. She stated that in 20–50% of GEP-NETs, conventional imaging does not identify the primary tumour.

Key points relating to imaging of GEP-NETs at different sites included:

- **pancreatic NETs**:
  - conventional imaging detects the primary tumour in 10–60% of cases
  - endoscopic ultrasound (90–100%) and angiography (40–75%) seem to be the most sensitive techniques
  - multiphase imaging is important
  - 3-D imaging can be advantageous
- **gastric NETs**:
  - minimal role for conventional imaging due to small size of tumours
- **hepatic metastases from NETs**:
  - angiography (81–96%) and magnetic resonance imaging (MRI; 55–70%) seem to be the most sensitive techniques
  - poor sensitivity for all modalities for tumours <5 mm
  - multiphase imaging is important
- **jejunal/ileal NETs**:
  - barium enema/enteroclysis rarely indicated
  - capsule endoscopy or double balloon endoscopy are promising
- **colonic NETs**:
  - colonoscopy is the gold standard approach
  - computed tomography (CT), colonography or MRI are indicated for staging, or if residual or metastatic disease is suspected.

Future techniques identified as being of interest included:

- contrast-enhanced multiphase ultrasound for pancreatic and hepatic lesions
- MRI using ultrasmall, superparamagnetic iron oxide, or gadolinium-labelled antibodies or peptides.

Radioisotope and functional imaging in GEP-NETs

Professor Rod Hicks *(Director, Centre for Molecular Imaging and Co-Chair Translational Research Group, Peter MacCallum Cancer Centre, Vic)*

Professor Hicks summarised molecular imaging and hybrid imaging approaches to the diagnosis of GEP-NETs. He identified planar imaging with ^{111}Indium-labelled octreotide ± single photon emission computed tomography (SPECT) as the current standard of care.

Key points made in relation to this method included:

- octreotide (an analogue of somatostatin) has a high affinity for somatostatin receptor subclass 2, which is expressed by most GEP-NETs
- the half life of ^{111}In-labelled octreotide makes it suitable for delayed planar and SPECT imaging
- intensity of uptake is measured on the 5-point Krenning scale, ranging from 0 (no uptake) to 4 (intense)
- octreotide scintigraphy is currently most useful for lesion characterisation and identifying tumours that are suitable for somatostatin analogue and radionuclide therapy (Krenning scale grade 3 and 4 tumours)
- a positive octreotide scan predicts the likelihood of a symptomatic response to somatostatin analogues in ~80% of cases (less so for a response to peptide radionuclide receptor therapy (PRRT)); a negative scan indicates suitability for chemotherapy rather than PRRT
- a therapeutic trial of a somatostatin analogue might still be reasonable in symptomatic patients who have a negative octreotide scan; however given that the likelihood of benefit is low, patients should be monitored carefully for response and consideration given to changing treatment if there is no evidence of benefit
- octreotide scintigraphy also has roles in diagnosis (including identification of the primary tumour and potential biopsy sites), as well as staging (either prior to resection or in patients with advanced disease).

Professor Hicks went on to describe a range of newer imaging modalities, including:

- the evolving role of fluorodeoxyglucose positron emission tomography **(FDG-PET)** and **FDG-PET/CT**:
  - FDG-PET avidity seems to be inversely associated with somatostatin receptor expression; increased avidity correlates with high Ki-67 staining and is associated with a poorer prognosis
  - FDG-PET avidity may predict for responsiveness to small cell lung cancer-type chemotherapy regimens
  - may be useful techniques for therapeutic monitoring
- benefits of **multimodality imaging**:
  - ^{111}In-octreotide SPECT/CT has advantages over planar imaging as co-registration allows the heterogeneity of somatostatin receptor expression in lesions to be appreciated
- new **positron emission tomography** (**PET) tracers**:
  - ^{68}gallium-labelled somatostatin analogues have been shown in preliminary studies to be superior to ^{111}In-labelled octreotide and have a longer shelf-life
  - tracers that focus on amine uptake pathways, eg ^{11}C- and ^{18}F-labelled 5-hydroxytryptophan (5-HTP) and FDOPA, are in development but are not yet available in Australia.

In closing, Professor Hicks concluded that:

- octreotide scintigraphy is the current standard of care and should be used if there is an intermediate-to-high likelihood of metastatic spread
- SPECT/CT is highly preferred and should be used if available

- SPECT with diagnostic CT could provide a 'one-stop shop' in the diagnosis of GEP-NETs
- the cost/rebate imbalance for radioisotope imaging needs to be addressed
- ^{68}Ga-somatostatin analogue PET has major logistic, diagnostic and cost advantages for sites with access to PET and sufficient patients to justify a generator
- consistency in molecular imaging technique is important when assessing progression, and imaging series for an individual should be undertaken by the same service wherever possible.

Loco-regional treatment of GEP-NETs

Professor Graeme Poston *(Director, Centre for Digestive Diseases, University Hospital Aintree, Liverpool UK)*

Professor Poston opened his presentation by highlighting the lack of high-level evidence on which to base decisions about loco-regional management of GEP-NETs. He stated that guidelines used at the Centre for Digestive Diseases are based on experience and level III–IV evidence.

Approaches to loco-regional treatment used in the UK for a range of GEP-NETs include:

- **type 1 gastric NETs** (usually small and multiple; rarely metastasise; 75% associated with chronic atrophic gastritis (pernicious anaemia); associated with achlorhydia and hypergastrinaemia; can develop iron-deficiency anaemia):
  - surveillance
  - endoscopic therapy (if small and few)
  - consider surgery (antrectomy) if patient has iron-deficiency anaemia
  - since these are gastrin-driven lesions, the recent availability of antigastrin therapy requires evaluation
- **type 2 gastric NETs** (associated with Zollinger-Ellison (ZE) syndrome; prognosis similar to Type 1 if ZE managed):
  - manage ZE syndrome and consider excising gastrinoma
  - consider excising gastrinoma as these lesions have a higher degree of malignancy
- **type 3 gastric NETs** (sporadic; usually solitary and >1 cm; associated with atypical carcinoid syndrome and histamine-induced flushing; behave similarly to gastric carcinoma):
  - manage as a gastric carcinoma
- **small bowel NETs** (often multiple and metachronous; often long-standing and misdiagnosed as irritable bowel syndrome (IBS); frequently metastatic at time of diagnosis):
  - conventional imaging has low sensitivity for detecting primary lesions, whereas functional imaging approaches such as ^{68}Ga somatostatin analogue PET/CT may be optimal for this purpose
  - resection of primary tumour(s) and lymph nodes (even in the presence of inoperable metastatic disease) increases long-term survival

- resection of the primary may be difficult due to: multiple primary tumours; high apical lymph node; desmoplasia; mesenteric varices and vessel encasement in fibrosis; anastomotic healing difficulty due to ischaemia
- surgery best carried out in experienced specialist centres by gastrointestinal surgeons knowledgeable in the management of NET disease

- **appendiceal NETs**: (most well-differentiated appendiceal NETs found incidentally during appendectomy; management depends on size and position):
  - tumour size is the most important factor determining prognosis, with metastases rare in tumours 2 cm or smaller
  - tumours <1 cm: appendectomy is adequate treatment and follow-up may not be required
  - right hemicolectomy is justified in tumours >2 cm, close to base, positive or unclear margins or with deep mesoappendiceal invasion
  - in patients considered cured after appendectomy or right hemicolectomy, a single serum CgA 6–12 months after surgery may be adequate follow-up
  - other patients may require follow-up at 6 and 12 months after surgery, and then annually thereafter involving clinical and biochemical testing and appropriate imaging
  - goblet cell carcinoids are a much rarer distinct clinicopathological entity with a greater malignant potential; hemicolectomy is standard treatment with follow-up similar to colonic adenocarcinomas
- **colorectal NETs**: (often found incidentally at endoscopy although rectal tumours may present early because of local symptoms; behave like carcinomas of the colon/rectum):
  - colonic NETs have the worst prognosis of any gastrointestinal NETs, often related to late stage at diagnosis
  - surgical management of localised tumours follows similar oncological principles to that of adenocarcinomas; endoscopic resection may be possible in rectal tumours <1 cm, whereas anterior resection is required for tumours >2 cm
  - in patients with metastatic disease, resection of primary disease may still be indicated as palliative management for tumour related obstruction
  - follow-up is required for all resected tumours >2 cm
- **pancreatic NETs** (subtypes include insulinomas, gastrinomas, glucagonomas, somatostatinnomas, and vasoactive intestinal polypeptide (VIP)-omas; the most common by far are insulinomas and gastrinomas; may be associated with familial syndromes (eg MEN1 and MEN2)):
  - pre-operative assessment includes appropriate imaging, biochemical assays for specific secretory products and special tests (eg gastrin provocation tests, 72-hour observed fast, plasma insulin to glucose ratio)
  - surgery is the preferred treatment but symptoms of hormonal excess should be treated optimally before resection is attempted
  - gastrinomas have a high propensity for malignancy; fasting gastrin levels or gastrin provocation tests may be diagnostic; gastric hypersecretion can be managed with histamine H2 antagonists or proton pump inhibitors; extent and type of surgery (eg enucleation/partial pancreatectomy/Whipples procedure) depends

on the size the tumour and location within the pancreas, but observation may be appropriate for occult tumours

  - insulinomas may be diagnosed by an observed 72-hour fast associated with hypoglycaemia or plasma insulin to glucose ratio above 0.3 and with an elevated plasma C-peptide level; endoscopic ultrasound, and intraoperative ultrasound or palpation may help in locating the tumour; laparoscopic surgery may be possible in some tumours localised preoperatively, whereas larger tumours may require more extensive surgery.

- **liver metastases**:
  - rules for potentially curative resection the same as for metastases from colorectal cancer
  - cytoreductive surgery may have a role in symptom control
  - need to consider health economics – cost of surgery versus cost of other therapies
  - limited evidence on which to base guidelines.

In conclusion, Professor Poston stated that:

- surgery remains the only (potentially) curative therapeutic modality for GEP-NETs
- only 20–30% of patients have disease that is amenable to potentially curative resection at presentation
- the evidence base for most surgical interventions remains weak and therefore recommendations are not strong
- surgical resections for GEP-NETS should only be undertaken in specialist centres under the direction of a multidisciplinary team.

During the discussion that followed Professor Poston's presentation, the potential role of somatostatin analogue therapy prior to surgery to prevent long-term mesenteric fibrosis was raised. Somatostatin analogues appear to have been effective in decreasing cardiac fibrosis but no evidence exists to confirm an effect on mesenteric fibrosis.

Is there a role for liver transplantation?

Professor Robert Padbury *(Director, Division of Surgical and Speciality Services, Flinders Medical Centre, SA)*

Professor Padbury discussed the role of liver transplantation in the management of GEP-NETs, prefacing his presentation by highlighting the small number of cases in which transplantation has occurred in Australia to date (n=6). He described the indications for liver transplantation in South Australia and compared these with the Mazaferro Milan criteria for liver transplant in patients with hepatic metastases,[8] which include:

- confirmed histological diagnosis
- primary drained by the portal system
- metastatic diffusion to the liver parenchyma of ≤ 50%
- stable disease
- age ≤ 55 years.

Data were presented for 24 patients (10% of whom were symptomatic) who received a liver transplant based on the Milan criteria, with a 5-year overall survival of 90% and 5-year disease-free survival of 77%.

Professor Padbury highlighted:

- the need to extend the endpoint beyond 5 years given the slow progression of GEP-NETs
- the question of what the outcomes would have been had patients not received a transplant.

Retrospective results were also presented from a French series of 85 patients who received a liver transplant for GEP-NETs,[9] with an overall survival of 48% and disease-free survival of 22% at 58 months. Professor Padbury noted that:

- the long time period for the study meant that it included patients receiving outdated assessments and treatments
- the outcomes do not meet the standard for transplant listing
- the study does provide the opportunity to assess prognostic indicators for transplantation in GEP-NETs.

Professor Padbury described how the Milan criteria have been adapted in South Australia:

- unresectable metastases
- complete resection of primary tumour at least 6 months prior
- no extrahepatic disease
- age < 50 years
- primary tumour in portal drainage area (exclude pancreas)
- exclude poorly differentiated tumours (low Ki-67 index)
- liver involvement < 50% (although it is acknowledged that this can be difficult to calculate using current imaging modalities).

In closing, Professor Padbury indicated that, based on these guidelines, few patients with GEP-NETs would be eligible for liver transplantation due to the presence of hepatomegaly and liver metastasis. He acknowledged that earlier detection and referral may influence the suitability of candidates for transplantation but concluded that the role of transplantation is limited in this indication.

Treatment of disseminated NETs

Professor Rod Hicks (*Director, Centre for Molecular Imaging and Co-Chair Translational Research Group, Peter MacCallum Cancer Centre****)***

Professor Hicks' second presentation focused on treatment options and considerations for disseminated GEP-NETs. He summarised the US NCCN guidelines and the algorithm used at the Peter MacCallum Cancer Centre, which is based on the ENETS guidelines. The NCCN guideline provides a range of treatment options and algorithms stratified on the basis of disease extent and biology.[6] The Peter MacCallum Cancer Centre algorithm relies on characterisation of both disease extent and tumour biology. This requires a multidisciplinary approach involving pathology, nuclear medicine, surgery, interventional radiology, medical oncology, endocrinology and cardiology.

Peter MacCallum Cancer Centre algorithm

(This algorithm assumes that all patients have been staged and characterised by biochemical diagnostic testing, conventional and functional imaging and biopsy confirmation of disease)

- Resectable? ⟶ **YES** – Surgery

  NO ↓
- Symptomatic/progressive? ⟶ **NO** – Observe

  YES ↓
- Octreotide-avid? ⟶ **YES** – Somatostatin analogue therapy + observation

  NO ↓ – PRRT if no response to somatostatin analogues
- Liver involved? ⟶ **NO** – Chemotherapy/biotherapy considered

  YES ↓ – Choice of chemotherapy depends on mitotic index

  – Palliative surgery

  – Liver-directed therapies (eg SIR-spheres®, chemo-embolisation)

The presentation covered a range of issues relating to current knowledge of systemic therapies, including:

- the need to clarify the potential anti-proliferative effect of somatostatin analogues in non-symptomatic, non-functional tumours
- discussion of preliminary data showing the benefit of SIR-spheres®
- the range of chemotherapy options based on tumour differentiation or proliferative grade:
  - streptozotocin + 5-FU/doxorubicin for low grade tumours
  - cisplatin/carboplatin + etoposide for high mitotic index (Ki-67 > 20%) or poorly differentiated tumours
- the potential role for newer agents including:
  - radiolabelled peptide therapies (benefits shown for octreotide labeled with ^{111}indium, ^{90}yttrium and ^{177}lutetium)
  - molecular targeted agents, such as anti-vascular endothelial growth factor (VEGF)/angiogenesis agents and inhibitors of mTOR (mammalian target of rapamycin); also anti-growth factor, anti-fibrosis and anti-serotonin agents
- the difficulty of measuring responses to systemic therapies given the heterogeneity of the GEP-NETs including:
  - difficulties of using standard criteria such as RECIST for these tumours
  - benefits of multimodal imaging technologies such as SPECT/CT for evaluating responses.

In concluding, Professor Hicks reiterated the importance of a multidisciplinary approach and flagged the importance of randomised controlled trials in determining optimal treatments. He indicated that there is strong rationale for combination treatment, and stated that further genomic characterisation will assist in identifying new therapeutic targets.

During the discussion that followed his presentation, Professor Hicks stated that meta-iodobenzylguanidine (MIBG) is no longer used at the Peter MacCallum Cancer Centre because it is less efficacious for treatment.

Follow-up and surveillance

Dr Gabrielle Cehic *(Nuclear medicine physician and oncologist, Flinders Medical Centre)*

Dr Cehic summarised the aims of follow-up and surveillance as:

- **for the individual**: evaluating the efficacy of therapy and assessing for disease progression or recurrence
- **at a population level**: identification of prognostic and risk factors.

Dr Cehic referred to published data from 35,825 GEP-NETs cases recorded in the SEER database to illustrate the benefits of surveillance and follow-up data and demonstrate the relationship between histological classification and survival. She went on to summarise information relating to surveillance and follow-up from the ENETS[4,5] and NCCN[6] guidelines.

Dr Cehic stated that standard surveillance for GEP-NETs is no different to the management of other malignancies:

- 3 months post-definitive resection: history and physical examination, biochemical markers and imaging
- 6-monthly to 3 years post-resection and annually thereafter: history and physical examination, and biochemical markers.

Particular issues relating to surveillance and follow-up of GEP-NETs included:

- the need for extended surveillance for patients with MEN-1 and 2 syndromes
- the need for heightened awareness/screening given that one quarter of patients will develop a second non-neuroendocrine malignancy (eg breast, colon or lung cancer)
- specific issues based on the GEP-NET site (eg the high risk of a gastrointestinal malignancy for patients with goblet cell pancreatic NETs)
- the need for assessment of quality of life issues as well as physical issues, especially for patients with functioning tumours
- the usefulness of general and specific biochemical markers in assisting with initial diagnosis and as indicators of the effectiveness of treatment and disease progression
- the potential prognostic value of biochemical markers.

CgA was described as the most universally useful general marker in GEP-NETs, with greatest sensitivity in the mid-gut NETs. However, the type of assay for CgA used may affect its usefulness, and levels of CgA can be altered by treatment with somatostatin analogues.

In discussing the choice of imaging tests used for surveillance and follow-up, Dr Cehic referred to previous presentations but highlighted:

- the importance of accounting for the lag period that can occur between changes on functional imaging and the anatomical changes that are measurable using conventional imaging
- the value of functional imaging in providing more real-time information with the choice of tracer determined by indication and availability.

In concluding, Dr Cehic recommended that follow-up and surveillance of GEP-NETs should reflect their biological and clinical heterogeneity, slow growth pattern and lack of

predictability. She stated that follow-up should include biochemical, anatomical and functional imaging measures, and cautioned against reliance on conventional imaging.

Living with GEP-NETs: a patient's perspective

Consumer representative

A GEP-NETs patient provided a personal perspective, sharing his story of how his own condition was diagnosed and managed. He described his international quest to determine the optimal treatment. Reflecting on his journey, he identified the importance of access to consistent and high-quality information on which to base treatment decisions. His story also provided an insight into the challenge of negotiating differing views and opinions from health professionals about optimal treatment strategies. He emphasised the need for specialist centres and consensus guidelines to guide treatment planning and delivery in Australia. He also identified the importance of information and education to support both patients and their practitioners, including the development of an Australian website.

In closing, the patient reiterated the importance of good communication and the value of the general practitioner in providing support during his journey.

Service planning and delivery

Professor Graeme Poston *(Director, Centre for Digestive Diseases, University Hospital Aintree, Liverpool UK**)***

In his second presentation, Professor Poston provided an overview of service delivery challenges and considerations encountered in the setup and management of a specialist GEP-NETs service in Liverpool in the UK. He listed the objectives of the service as:

- offering the highest possible standards of care to GEP-NET patients
- providing agreed management pathways
- data management
- demonstrating outcomes live in real time
- clinical trials
- securing funding for treatment
- education.

Problems encountered in setting up the service related to the uncommon nature of GEP-NETs and the resulting low priority placed on the disease by health service administrators. Professor Poston also flagged the potentially high cost of care, given both the cost of treatments and the demand on services over several years.

The Liverpool service covers a catchment of around 6 million people within a 150 km radius and has 1–2 referrals per week. The service incorporates a multidisciplinary team comprising:

- surgery (site-specific)
- nuclear medicine
- oncology
- interventional radiology
- endocrinology
- nursing.

The team meets fortnightly and discusses new patients, patients completing treatment and patients who have had recent repeat scans. All attendees are documented and decisions are recorded in the patient's case notes with referring clinicians informed in writing. The central function of GEP-NET nurse specialists in the team was described, with roles including:

- management (of MDT meetings and service delivery)
- clinical care (symptom control, liaison and information)
- research (database and range of studies)
- education (health professional, patient and community).

Professor Poston identified the key diagnostic and treatment requirements of the service and emphasised the importance of guidelines and pathways to guide management and patient care. Data management was identified as a crucial aspect of the service, driven in part by legislation in the UK requiring clinicians practicing in oncology to be able to generate outcome data. Issues flagged in relation to data management included:

- the need for a minimum data set at referral
- the importance of prospective storage of data
- the ability to demonstrate adherence to guidelines and real time outcomes
- the importance of peer review
- the use of data as a prospective base for clinical research.

The minimum data set on referral is currently collected on paper and includes information relating to the date of referral, the individuals involved, background information and test results. This paper-based system is being trialled as an electronic Access database that will allow the collection and assessment of data in real time.

Professor Poston provided an overview of the group's research interests, including:

- metastatic carcinoid disease & fatigue
- EORTC quality of life fatigue module development
- EORTC quality of life GI-NET module development
- NET-One: chemotherapy and non-functioning non-resectable PNETs
- Ipsen Somatuline® (lanreotide) Autogel® study for non-functioning NETs
- toxicity effects of radio-labelled therapies
- patient satisfaction survey.

He highlighted the importance of funding in maintaining the service and achieving best outcomes. Issues included:

- the fact that funding is applied for on a single patient basis
- the wide catchment area of referrals
- the lack of uniform categorisation of drugs with some drugs restricted to delivery in a hospital setting.

Other important factors included education about GEP-NETs within both the hospital and community setting and across disciplines and the role of industry in raising awareness of the condition.

In concluding, Professor Poston indicated that setting up a multidisciplinary service for the management of patients with GEP-NETs is feasible but that it requires integration across specialties and the provision of multi-modal therapies. He highlighted the benefits of the service as a resource for education and research and stressed the benefits of an integrated approach with industry in achieving the service's aims.

In the discussion that followed his presentation, Professor Poston identified the importance of a national lead and industry support in driving national policy around GEP-NETs management. He also emphasised the importance of keeping guidelines simple to encourage uptake, with further detail based on individual GEP-NETs provided as a second level. He also emphasised the importance of defining a minimum standard of care with sufficient flexibility to allow tailoring to the needs of the individual.

In describing the acceptance in the UK of centres of excellence, Professor Poston stated that, for rare conditions such as GEP-NETs, support has been high. He identified additional enablers to encourage uptake such as identifying the risks to both the individual and the health service for non-specialist involvement in the management of GEP-NETs and the important role of patient advocates in driving the need for centres of excellence.

Plenary discussion

During the plenary discussion that followed the presentations, a range of issues were raised, including:

- the need for improving the accuracy of biochemical and molecular markers for GEP-NETs and the development of novel markers
- appropriate models for 'centres of excellence' within the Australian setting, given the country's broad geography, lack of health funding for emerging treatments, and mix of public and private service delivery; options discussed included the use of telemedicine and the possibility of a 'virtual centre'
- the importance of collecting pooled national data, for example through the development of a national registry or database, regardless of the model of service delivery applied
- the importance of involving individuals with expertise in business planning and modelling to guide approaches and ensure best returns on investment
- the importance of involving all relevant stakeholders in planning and implementation, including specialist and generalist health professionals, patients, health service administration, scientists and industry representatives.

WORKSHOP OUTCOMES

PRIORITIES FOR CHANGE

Each participant was asked to identify two key priorities for improving the management of GEP-NETS in Australia. Priorities were sorted thematically and key themes reported back to the plenary group.

A full list of the priorities identified is provided in Appendix III. Key themes are outlined below:

- consensus on national **guidelines/pathways** to guide diagnosis, treatment, surveillance and follow-up with the aim of standardising care
- importance of **early recognition of** GEP-NETs and **individualisation** of care
- agreement on the model and role of **centres of excellence** and how these could be implemented in Australia, considering issues of access for regional/rural patients
- importance of national **data collection**, including identification of a minimum data set and implementation and utility of an accessible national database
- importance of **multidisciplinary care** and the role of individual practitioners within the team, including the role of specialist GEP-NET nurse coordinators
- **funding** for diagnostic and treatment technologies and resources required for optimal management of GEP-NETs, and better **understanding of how to advocate for change**
- processes for ensuring sharing of **information,** including access to information about the availability of specialists and referral pathways, as well as a national website about management options for patients and health professionals
- options for research and processes for agreeing a **national research agenda**
- access to **new technologies**
- potential role of a GEP-NETs **special interest group** with links to international societies.

ISSUES AND RECOMMENDATIONS

Participants were asked to consider four issues:

1. Diagnosis, monitoring and surveillance

- A minimum investigation set, including histopathological testing and serum markers
- Staging (including imaging) and risk stratifying patients
- Monitoring treatment response and surveillance strategies for disease recurrence

2. Locoregional treatment

- What are the aims of surgery in GEP-NETs?
- The use of liver-directed therapies (chemo-embolisation, SIR-Spheres®, radiofrequency ablation and cryotherapy)
- Is there a role for liver transplantation?

3. **Systemic treatment**
    - Should somatostatin analogues be used in patients with non-functioning or asymptomatic GEP-NETs?
    - Which patients may benefit from chemotherapy (cytotoxics and targeted agents), and which agents/regimens?
    - Selecting patients for and improving access to radionuclide treatment
4. **Service delivery planning**
    - Should treatment of GEP-NETs occur in specialised centres?
    - Setting management guidelines and standards
    - Increasing patient access to optimal multidisciplinary care
    - Problem areas, hurdles and short falls

Issues and recommendations were identified through discussion by small pre-allocated multidisciplinary groups, followed by consolidation and refinement by the plenary group. Time limitations precluded a full consensus approach and the outcomes reported below summarise areas of convergence reported back to the plenary group.

Diagnosis, monitoring and surveillance

Key questions	Issues
Defining a minimum investigation set	• Lack of agreed diagnostic criteria (pathology) • Lack of understanding of serum markers, including what tests should be done and where • Role of a central database for collection of information
Staging and risk stratification	• Lack of agreed staging systems • Lack of/inconsistent availability and access to scans, eg octreotide scintigraphy, endoscopic ultrasound, ^{68}Gd-PET • Role of genomics • Role of PET, including cost issues and restricted indications • Role of multidisciplinary teams and centres of excellence in staging
Monitoring and surveillance	• Lack of consensus about frequency of investigations and follow-up tests • Should monitoring be linked to the stage of disease/prognosis?

Recommendations

- **Diagnosis** should follow the ENETS guidelines for pathology, incorporating:
    - agreement on which serum markers should be used, including general and site-specific markers
    - consideration to adopting ENETS proposed TNM staging and grading (based on mitotic count and Ki-67)
    - use of synoptic reporting
    - notification to a central database/registry
    - collation of samples as part of a national tissue bank.

- All patients with a GEP-NET should be discussed pre-operatively/pre-treatment by a **multidisciplinary team**, including discussion of staging/grading information.
- **Staging** should be individualised based on the site of the GEP-NET and undertaken by a specialist centre with access to optimal imaging technologies including:
  - triple-phase CT scan
  - ultrasound/endoscopic ultrasound
  - SPECT/CT
  - MRI
  - octreotide scintigraphy
  - echocardiograms
  - trials to evaluate emerging technologies.
- A **national database** of GEP-NETs information should be developed, with consideration given to the need for legislation and audit.
- A national **tissue bank** should be established to facilitate translational research in GEP-NETs.
- Monitoring and follow-up should be **individualised** to the patient and:
  - utilise imaging and serum tumour markers
  - reflect the site and stage of disease, rate of disease progression and treatments the patient has received (eg somatostatin).

Issues raised during the plenary discussion that followed the report back included:

- the need for agreement and uniformity on methods of coding GEP-NETs and the importance of engaging with the Australasian Association of Cancer Registries (AACR) to facilitate agreement and reporting
- the distinction between registry-level data and more detailed outcomes and quality-of-life data, and consideration of options for populating a more detailed database, drawing on examples from other medical settings such as orthopaedics
- the importance of engaging the Royal College of Pathologists of Australasia (RCPA) to gain agreement and consistency in pathology reporting for GEP-NETs
- consideration of the role of primary care in screening, diagnosis and referral
- how to address the conflict between best practice and availability of government rebates, eg lack of adequate access and reimbursement for appropriate functional imaging, and lack of reimbursement for MRI testing to assess hepatobilliary metastases
- the importance of ensuring that the model of centres of excellence does not exclude regional sites with an interest and expertise in managing these patients
- the importance of developing an algorithm that can be used to guide monitoring and follow-up plans based on level of risk to optimise the chance of locoregional salvage if disease is found.

Reflecting on the discussion, Professor Modlin suggested that a question on GEP-NETs could be incorporated into general practice training examinations to increase the level of awareness of this group of tumours. He also emphasised the importance of health economics data in determining decisions about what tests and care are affordable compared with the potential consequences of not providing optimal care.

LOCREGIONAL TREATMENT

Key questions	Issues
Aims of surgery	• Identify the primary tumour • Curative treatment (if possible) • Symptom control • Palliative care role is important • Surgical approach may be influenced by cardiac assessment and nodal involvement • Important to identify patient aims • May require a two-staged approach
Use of liver-directed therapies, eg SIR-spheres®, chemoembolisation, TACE, peptide-directed therapies	• Little or no data from randomised controlled trials on which to base guidelines • Lack of agreement of timing of therapies and which patients therapies are suitable for • Availability of therapies and expertise is variable • Cost of therapies must be considered • Difficult to develop consensus but can provide options • Important to consider patterns of care
Role of liver transplantation	• Limited availability of donors for transplantation • Cadaveric versus living related transplants • Issues of outcome vs experience

Recommendations

- **Surgery** should be undertaken by a specialist within a high-volume centre and should include:
  - multidisciplinary input to workup, including CgA and octreotide scintigraphy
  - cardiac assessment
  - centralised tissue banking
  - consideration of the role of somatostatin analogues to reduce mesenteric fibrosis and cardiac complications.
- The requirement for **liver-directed therapies** should be determined by a multidisciplinary team with therapies delivered by health professionals experienced in their use:
  - outcomes of treatment with liver-directed therapies should be recorded on a national database to guide future care.
- **Clinical trials** of liver-directed therapies should be undertaken:
  - 'rare tumour funding' should be sought from Federal Government to support centres of excellence and drive the discovery of novel therapies.
- There are inadequate data to justify recommending **liver transplantation** as standard treatment for patients with GEP-NETs.

Issues raised during the plenary discussion that followed the report back included:

- the need to determine best practice guidance in the absence of data from randomised clinical trials
- the importance of international collaborative studies to gain sufficient patient numbers from which conclusions can be drawn
- the challenge of determining outcomes from studies given the slow disease progression
- the importance of considering patient preference and quality of life issues as well as seeking to prolong life
- the potential risk of stimulating cell growth through increasing growth factors during palliative liver resection.

Comments provided by Professor Poston and Professor Modlin following the discussion included the ethical issues of undertaking randomised controlled trials involving surgery, given the known benefits of surgery for this disease and the potential use of a Delphic process to help bridge the gap where consensus on recommendations is not possible.

SYSTEMIC TREATMENT

Key questions	Issues
Use of SSAs in patients with non-functioning/asymptomatic GEP-NETs	• Funding issues given that octreotide is reimbursed only for symptomatic patients • Importance of gauging the pace of progression and tumour differentiation • Requirement for more data regarding the potential antiproliferative effect of somatostatin analogues in non-functional/non-octreotide avid tumours
Use of chemotherapy	• Some evidence of benefit of cytotoxics prior to surgery for functional progressive disease • Lack of data regarding the benefit of adjuvant treatment • Role of cytotoxics will vary according to rate of proliferation – likely to be beneficial for tumours with a high mitotic index • Range of cytotoxics still at trial stage
Radionuclide treatment	• Use of radio-isotopes dependent on somatostatin avidity of tumours, rate of progression and co-morbidities • Issues with access to and funding of radio-isotopes, eg ^{177}Lu, ^{111}In and ^{90}Y • Need for randomised controlled trials to generate data regarding survival and radio-sensitisation

Recommendations

- Based on current evidence, **somatostatin analogues:**
  - should be used in symptomatic functional GEP-NETs
  - cannot be recommended for use in non-functioning (non-octreotide avid) GEP-NETs until further supportive evidence is available
  - may be helpful in patients with progressive disease.

  Recommendations should be reviewed in light of outcomes from clinical trials.
- **Chemotherapy** has a role in the treatment of GEP-NETs with the choice of treatment dependent on the rate of proliferation:
  - 5-FU and streptozotocin for progressive disease with a low mitotic index/Ki-67
  - carboplatin/cisplatin + etoposide for high-grade disease
  - await trial results for experimental treatments (bevacizumab, anti-VEGF, mTOR inhibitors, IGFR-1 inhibitors).
- **Radionuclide** therapy may be an alternative treatment after progression on somatostatin analogues and should take account of tumour somatostatin avidity and other patient factors including co-morbidities and renal/hepatic function.
- Formal trials of radionuclide therapy are required to determine survival and optimal radiosensitisers.

Issues raised during the plenary discussion that followed the report back included:

- the need for consistent terminology regarding what is meant by a 'functioning' tumour, ie octreotide avid or secreting peptides
- whether additional patients may benefit from octreotide treatment outside PBS indications, eg patients with functioning, asymptomatic, non-resectable disease
- the role of MIBG – it was highlighted that MIBG is not an effective therapy despite high uptake by tumours because the delivery of radiation to the tumour is relatively ineffective; however it was recognised that it may have a role in centres without access to more effective radionuclides
- the importance of making guidelines concise and clear for use by a range of health professionals
- the role of long-acting somatostatin analogues in limiting or inhibiting the progressive growth of somatostatin-expressing cells
- the lack of infrastructure in many hospitals to provide peptide therapies and the importance of ensuring that specialist centres have access to therapies that show optimal outcomes.

SERVICE DELIVERY PLANNING

Key questions	Issues
Should treatment occur in specialist centres?	• 'Centre' implies a comprehensive cancer centre – consider other terminology, eg 'group' or 'network' • Importance of meeting the needs of patients in regional and rural settings as well as public/private service delivery and the need for coordination of care • Options for a virtual centre with communication back to local providers for delivery of care • Importance of gaining buy-in from key stakeholders • How to define core competencies of specialist centres • Issues of state and federal boundaries regarding infrastructure and funding • Role of a central body to collect data
Setting management guidelines/standards	• Do not duplicate existing standards • Who will undertake adaptation of existing international guidelines? • Endorsement by professional bodies and groups can be valuable • Important to reflect the need for individualised care
Increasing access to multidisciplinary care	• Likely to flow on from the implementation of 'centres of excellence' and guidelines • Will require funding • Referral pathways, information and education of clinicians will be essential • Appropriate coordination will be essential, eg through nurse coordinator
Problem areas, hurdles and short falls	• Funding issues, including national and state-based funding • Patient 'ownership' issues • Public and private service delivery challenges

Recommendations

- There is general agreement on the need for a **centralised source of specialist expertise** to guide the management of GEP-NETs, but how this is applied to the Australian setting in terms of actual sites versus virtual networks and the number of 'centres of excellence' required remains to be determined.
- **ENETS guidelines** should be adapted for Australia and New Zealand with input and endorsement from key stakeholder groups. Guidelines should reflect the need for individualised assessment and treatment and should be presented in a concise format for ease of use.
- The **NCI Summit Conference recommendations**[7] may be utilised, where applicable, to provide a basis for defining priorities and guiding investigative, educational and management strategies in NET disease.

- **Care coordination** and **defined referral pathways** will be important components of the service delivery model, requiring:
  - funding of NET nurse specialist positions
  - web-based information about available services and referral pathways
  - education of health professionals.
- The successful implementation of strategies will require **funding**, **engagement of relevant stakeholders** and **collaboration**.
- Funding should ideally be derived federally in order to overcome the current limitations of the state-based health systems.
- An 'inner circle group' should be established to interface Australian priorities in management with international developments.

Issues raised during the plenary discussion that followed the report back included:

- the challenge of balancing patient and clinician preference for local care with the benefits of providing care in a high throughput centre with skills and experience in the management of GEP-NETs
- the importance of defining a functional hub and spoke model of service delivery that ensures appropriate care
- the need to consider population size and health economic data when planning centres of excellence.

Reflecting on these discussions, Professor Modlin reiterated international views on the importance of centres of excellence and suggested a two-level model, in which sophisticated treatments and technologies are available at level 1 sites, with level 2 sites providing some care based on expertise. He highlighted that criteria for centres of excellence, including the number required based on population size, will soon be in development in the US. Professor Poston alluded to the UK 'Map of Medicine' initiative for funding pathways to care. This is currently limited to common tumours but will be extended to NETs and rarer tumours in due course.

CONSUMER PERSPECTIVE

Brian Gibson

In reflecting on the outcomes of the workshop, Mr Gibson expressed his support for the collaborative approach and emphasised the importance of patients with GEP-NETs having access to the right advice and appropriate care. He indicated his support for the establishment of centres of excellence and broader sharing of information.

WHERE TO FROM HERE

Professor David Goldstein *(President, COSA)*

Professor Goldstein identified the commitment of COSA, ANZHPBA, AGITG and ANZSNM to review the outcomes from the workshop and agree a pathway to take the recommendations and outcomes forward. He indicated that key steps would include:

- engagement of relevant stakeholders, including pathologists
- piloting recommended approaches
- facilitating ongoing communication and collaboration.

In closing, Professor Goldstein thanked the participants, Executive Committee and sponsors for their support and interest and encouraged ongoing interaction and commitment to improve the management of GEP-NETs in Australia.

CLOSING THOUGHTS

After the close of the workshop, the international speakers provided a personal perspective about the workshop outcomes. Professor Poston's comments reflected the evolving nature of health service change and the need to allow sufficient time to implement new strategies and approaches. Recognising the value of a collaborative approach involving all relevant stakeholders, Professor Poston paid tribute to the commitment to change demonstrated by workshop participants.

Professor Modlin reviewed key outcomes from the workshop and identified some areas that had not been covered in depth. He emphasised the importance of centres of excellence in ensuring best practice and the importance of stakeholder engagement and lobbying of health service administrators to drive change. Professor Modlin also recommended that some thought be given to screening tests as well as improving awareness of GEP-NETs within the community to enhance early detection of these tumours.

ACKNOWLEDGEMENTS

The workshop was sponsored by unrestricted educational grants from Ipsen Pty. Ltd. (Gold Sponsor), Novartis Pharmaceuticals Australia (Silver Sponsor), SIRTeX Medical (Bronze Sponsor) and the ANZHPBA (Bronze Sponsor).

COSA gratefully acknowledges the input and support of the workshop facilitator, Mark Douglas from ETHOS Australia and the convenor and members of the Workshop Steering Committee:

- Dr Yu Jo Chua (workshop convenor)
- Professor David Goldstein (COSA)
- Dr Robert Padbury (ANZHPBA)
- Professor John Zalcberg (AGITG)
- Professor Rod Hicks (ANZSNM)
- Dr Gabrielle Cehic
- Dr Susan Neuhaus
- Dr Peter Cosman
- Dr Michael Hirshorn (consumer representative).

COSA would also like to thank the workshop presenters Dr Kate Moodie, Professor Rod Hicks, Dr Robert Padbury, Dr Gabrielle Cehic, and in particular international speakers Professor Irvin Modlin and Dr Graeme Poston.

The workshop report was developed by Dr Alison Evans from Alison Evans Consulting.

REFERENCES AND FURTHER READING

1. Modlin IM, Lye KD, Kidd M. A 5-decade analysis of 13,715 carcinoid tumors. *Cancer* 2003;97:934–59.
2. Chua YJ. Personal communication.
3. Modlin IM, Oberg K, Chung D et al. Gastroenteropancreatic neuroendocrine tumours. *Lancet Oncol* 2008;9:61–72.
4. De Herder W, O'Toole D, Rindi G, Wiedenmann B (Eds). ENETS Consensus Guidelines for the Management of Patients with Digestive Neuroendocrine Tumors. Part 1 – Stomach, Duodenum and Pancreas. *Neuroendocrinology* 2006; 84(3):151–216.
5. De Herder W, O'Toole D, Rindi G, Wiedenmann B (Eds). ENETS Consensus Guidelines for the Management of Patients with Digestive Neuroendocrine Tumors. Part 2 – Midgut and Hindgut Tumors. *Neuroendocrinology* 2008;87(1):1–64.
6. National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology: Neuroendocrine Tumors. 2007. http://www.nccn.org/professionals/physician_gls/PDF/neuroendocrine.pdf (accessed online 30 July 2008)
7. Modlin I, Moss S, Chung DC et al. Priorities for improving the management of gastroenteropancreatic neuroendocrine tumors. *J Natl Cancer Inst* 2008;100:1–8.
8. Mazzaferro V, Regalia E, Doci R. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *N Engl J Med* 1996;334:693–700.
9. Grégoire E, Le Treut YP, Belghiti J et al. Primary tumor site and liver size are predictors for survival after liver transplantation for endocrine metastases. A 85-case french multicentric report. ILTS Meeting, Rio de Janeiro, June 20–23, 2007.

FURTHER READING

Oberg K, Kvols L, Caplin M *et al*. Consensus report on the use of somatostatin analogs for the management of neuroendocrine tumors of the gastroenteropancreatic system. *Ann Oncol* 2004;15:966–973.

Ramage JK, Davies AHG, Ardill J *et al*. Guidelines for the management of gastroenteropancreatic neuroendocrine (including carcinoid) tumours. *Gut* 2005;54:1–16.

Kulke M. Clinical presentation and management of carcinoid tumors. *Haematol Oncol Clin N Am* 2007;21:433–455.

APPENDIX I: WORKSHOP PROGRAM

AUSTRALIAN NEUROENDOCRINE TUMOURS (NETS)
CONSENSUS WORKSHOP
MEETING MANAGEMENT CHALLENGES IN AUSTRALIA
8:45am – 4:30pm
Monday 28 July 2008
Hilton Hotel, Melbourne Airport
Facilitator: Mark Douglas

8:30-8.45 am	Registration	
8:50	Welcome and introduction	*Professor David Goldstein*
9.00	NETS: the story so far	*Professor Irvin Modlin*
9:30	Conventional imaging in NETs	*Dr Kate Moodie*
9:45	Radioisotope and functional imaging in NETs	*Professor Rod Hicks*
10:00	Loco-regional treatment of NETs	*Professor Graeme Poston*
10:30	**Morning Tea**	
10:45	Is there a role for liver transplantation?	*Professor Robert Padbury*
11:00	Treatment of disseminated NETs	*Professor Rod Hicks*
11:15	Follow up and surveillance	*Dr Gabrielle Cehic*
11:30	Living with NETs: a patient's perspective	*GEP-NETs patient*
11:45	Service planning and delivery	*Professor Graeme Poston*
12:15	Questions/discussion	*All*
12:30pm	**Lunch**	
1:30	Breakout Groups: Round table discussions	*Mark Douglas*
3:30	**Afternoon Tea**	
3:45	Review of outcomes and recommendations • Diagnosis, monitoring and surveillance • Locoregional treatment • Systemic treatment • Service delivery planning	*Mark Douglas*
4:15	Where to from here?	*Prof David Goldstein*
4:30	CLOSE	

APPENDIX II: LIST OF ATTENDEES

Name	Discipline
Mark Appleyard	Gastroenterologist
Kathy Ansell	COSA
Eugeni Ashby	Nuclear medicine
Andrew Barbour	Surgeon
Peter Barry	Surgeon
Roger Berry	Surgeon
Lourens Bester	Radiologist
Tony Bonaventura	Medical Oncologist
Joyce Bonello	Care Coordinator
John Burgess	Endocrinologist
Lisa Busskohl	SIRTeX Medical
Carol Cameron	Care Coordinator
Gabrielle Cehic	Nuclear Medicine
Yu Jo Chua	Medical Oncologist
Phillip Claringbold	Medical Oncologist
Stephen Clarke	Medical Oncologist
Phil Clingan	Medical Oncologist
Mark Cullinan	Surgeon
David Currow	Cancer Australia
Dragan Damianovich	Medical Oncologist
Feroz Dean	Novartis
Paul Desmond	Surgeon
Hugh Dixson	Gastroenterologist
Malcolm Douglas	Surgeon
Emma Duncan	Endocrinologist
Peter Evans	Surgeon
Robert Finch	Surgeon
David Fletcher	Surgeon
Jason Free	Surgeon
Jon Gani	Surgeon

Name	Discipline
Brain Gibson	Consumer
David Goldstein	Medical Oncologist
Koroush Haghighi	Surgeon
Rod Hicks	Nuclear Medicine
Michael Hirshorn	Consumer
Warrick Inder	Endocrinologist
Michael Jefford	Medical Oncologist
Robert Jones	Surgeon
Chris Karapetis	Medical Oncologist
Sandra Kemp	Clinical Nurse Consultant
Ian Kirkwood	Nuclear Medicine
Michael Kitchener	Nuclear Medicine
Jonathan Koea	Surgeon
Dusan Kotasek	Medical Oncologist
Winston Liaux	Medical Oncologist
Robert Mansberg	Nuclear Medicine
Helen McDade	Care Coordinator
Margaret McJannett	COSA
Michael Michael	Medical Oncologist
Irvin Modlin	Consultant Surgeon
Kate Moodie	Radiologist
Melinda Munns	Ipsen Pty Ltd
Bill Murray	Pathologist
Susan Neuhaus	Surgeon
Sam Ngan	Medical Oncologist
Robert Padbury	Surgeon
Venkat Parameswaran	Scientist
Graeme Poston	Consultant Surgeon
Tim Price	Medical Oncologist
David Ransom	Medical Oncologist
Meg Rogers	Care Coordinator
Candice Sagi	Medicine V

Name	Discipline
Jas Samra	Surgeon
Eva Segelov	Medical Oncologist
Jenny Shannon	Medical Oncologist
Nimit Singhal	Medical Oncologist
Mark Smithers	Surgeon
Andrew Snarski	Nuclear Medicine
Joanna Snarski	Nuclear Medicine
Anthony Speer	Gastroenterologist
Andrew Strickland	Medical Oncologist
Edwin Szeto	Nuclear Medicine
Mark Taylor	Ipsen Pty Ltd
Ben Thomson	Surgeon
David Torpy	Endocrinologist
Coral Tudball	Nuclear Medicine
Harvey Turner	Nuclear Medicine
Marius van den Berg	SIRTeX Medical
Eva Wegner	Nuclear Medicine
Ron Weiner	ANSTO
David Wyld	Medical Oncologist
Desmond Yip	Medical Oncologist
Rosemary Young	Medical Oncologist
John Zalcberg	Medical Oncologist
Allan Zimet	Medical Oncologist
Adam Zwart	Novartis

APPENDIX III: PRIORITIES FOR CHANGE – INDIVIDUAL PRIORITIES

Listed below is the complete list of priorities for change identified by individual workshop participants.

Topic	Priority
Standardisation/guidelines /pathways	**Diagnostic** • Education position re: chromogranin and staging to promulgate widely across medical community • Standardisation in diagnostic and follow-up imaging and a clear pathway of what tests to do, when • Standardisation of histopathology techniques, staining methods and reporting • Standardisation of chromogranin A assays and more sites offering this test to allow shorter turnaround time • Standardise diagnostic tests • Recommended minimum work-up of patients with NET (then process from there) • Minimum diagnostic tests for diagnosis and surveillance • Guidelines for use of medical imaging and nuclear medicine in diagnosis and follow-up • Improved support/infrastructure/guidelines for private radiology/diagnosis for NETs in regional areas
	Treatment • Guidelines for appropriate use of radionuclide treatment – which and when? • Published consensus for NET management to be reviewed by expert panel every few years (direct readers to website for regular updates?) • Develop consistent guidelines for treatment • Recommendations for use of SSAs and radiolabelled therapies • Define indications for surgical intervention and observation in patients with liver disease • Agreed clinical algorithms for diagnosis, treatment and follow-up • Australian national treatment algorithm - where do I send patients, for what and how do I find that? • Establish standards for surgery: indications and technique • Systemic treatment – clear guidelines for management in rural areas • Treatment pathway • Guidelines for TCE
	Follow-up/surveillance • Frequency of follow-ups of CgA estimation during medical management and post-surgery • Protocol guidelines for surveillance investigations • Guidelines for follow-up of those patients who in many cases live for years – bloods and scans – how often? • Establish protocols for follow-up after potentially curative resection

Topic	Priority
	• Specific recommendations for follow-up after curative resection, eg 3-monthly CgA, 12-monthly octreotide
	General • Agreement to progress national consensus • Concise over document for Australia and New Zealand • Consensus document • Consensus of general management approaches • National database of pathways for clinicians and patients • National guideline • A set of monograph guidelines with defined areas of flexibility • Flow diagram of management • Guidelines for minimal standards so that those Drs in private practice who refuse to commit or contribute to a specialised centre will at least have a set of suggestions to improve their practice at a national consensus level
Centre of excellence	**General** • There should be one centre of excellence for diagnosis and treatment of NETs. A follow-up treatment plan could be developed and where possible ongoing treatment monitored. • Develop centres of excellence • Develop centres of excellence • Approaches for concept of specialist centres and outreach services • Centres of excellence with a focus on data collection and clinical trials will be beneficial for physicians, patients and industry • Centres of excellence with MDTs in major centres in Australia • Creation of specialist centres • Centralisation of clinical services • Establishing centres of excellence in each capital city • Centres of excellence in Australia for this disease – perhaps 3 • Establish a single centre of excellence for management of NET in each state capital city • Centre of excellence with funding and world class technology • Consensus that specialised centres can be established with linkage to ensure distant engagement of all practitioners • Each state should form a centre of excellence • Centres of excellence (national)
	Logistics • Funding and decision on establishment of a limited number of centres of excellence • Agreed protocols for centres of excellence • Government support for state-based MDT/Centre of excellence – some states may have 2 • Central Federal funding for centre of excellence in each capital city for NET management and R&D • What is the best model in Australia for centres of excellence? • Integration of regional centres into the centre of excellence

Topic	Priority
	• Agreed population denominator for feeder population of specialised centre • Define core capabilities for NET centre of excellence • All 'carcinoid/NET' pathology should be reviewed by one of a few accredited pathology referral centres
	Virtual Centre of excellence • Have an accessible treatment centre – 'centralised' accessible via tele- and videoconference • Setting up of a virtual centre of excellence • Establish state-wide NET services at centre of excellence or virtual network with government funding support
Data	**Database** • Database for research • National database on NET • Method of facilitating data collection, noting legal/consent issues – do we need a UK style requirement? • Prospective web-based GEP-NET national registry of interested professionals and patient database • There should be a registry combined with open-source open-access clinical trials/research • Establish a national register for NETs • A centralised data collection centre/service with local access to information • Centralised database for NETs • Better collection of data so as to increase the knowledge of disease progression • As there are small numbers, require comprehensive collection of comprehensive data about diagnosis/management – nationally held data • A national database of diseases and treatment outcomes • Develop Australasian mechanism to record data and discuss patients with NETs • Implementation of prospective database • Centralised database for NETs
	Data set • Establishment of simple minimum data set and database for GEP NETs • Creation of data set for use by 'expert' centres • Agreed team to develop agreed data set to be collected prospectively
	Use of data • Create a system for data collection and research to determine if new/invasive therapies alter symptoms and survival in a prospective manner • Establish a nationwide database for collection of outcomes with the aim of standardising treatment • Prospective data analysis of cases by each MDT with regard to treatment outcomes so that the value of emerging treatments can

Topic	Priority
	be ascertained • There should be a national report on NETs using the SEER criteria to determine whether incidence, mortality and survival patterns are the same in Australia compared to the US
Multidisciplinary care	**General** • Develop a generic template for a NET multidisciplinary team • A simple one-stop multidisciplinary clinic to allow for specialised service delivery • Multidisciplinary clinic for access to data and treatment Australia-wide – virtual landscape? – government funding? The concept of videoconferencing has not worked well so far in radiology • Patients should have multidisciplinary care – local MDT with video-link access to major centre • Patients should have multidisciplinary care (but I can't possibly squeeze in another MDT meeting – and I see a lot of this disease!) • Greater focus on multidisciplinary management of patients • Incentives and guidelines to start NET MDM at each tertiary hospital – say 1-2/state • NET MDTs established in major centres with direct contact with local affiliates to manage patients • Treatment decisions and management should be made with the context of a resourced appropriately skilled multidisciplinary team • Requirement of MDT (formal approach)
	Specific roles • Any guidelines that emerge in addition to medical management for this population of patients should include their supportive care and psychosocial needs • Promote the importance of a specialist nurse as a vital part of MDT in Australia • Patient referred to cancer nurse coordinator at the point of diagnosis/consultation with specialist • Pathologists need to be involved in the discussion re management of these tumours • Operability should be judged by surgeons
Funding	**Diagnostic** • Medicare funding for Octreoscan® be increased and inclusive of a wider range of indications. Currently we are splitting the dose into two or three to make the scan cost effective and mitigate losses but at the cost of reducing diagnostic accuracy • Industry to be asked to fund investigations (similar to companies paying for HER/K-ras testing) • Federal funding of diagnostic modalities (PET/CT, SPECT/CT, C11-PET, FDOPA, MRI, EUS) • Funding for basic imaging in NETs, ie Octreoscan®, MRI etc through Medicare • Funding for functional imaging for NETs ie PET scan, DOTATOC etc
	Treatment • Special funding for essential management procedures, eg

Topic	Priority
	expensive nuclear medicine technologies – PET and radionuclide therapy • Federal funding of radionuclide therapy • Funding of therapeutic indium-octreotide ablative therapies • Funding for PRRT therapy • Determine the best process for obtaining the necessary funding for the various therapeutic options • We need to be able to offer PRRT and SIR Spheres to these patients in at least one centre of excellence in each state. We need Federal funding • Commonwealth approval for peptide radionuclide therapy reimbursement
	Resources • Funding for nurse practitioners in NETs • Obtain funding for nurse specialists • Make nationally available access to subspecialist advice (tele- or face-to-face) and funding for that process through Medicare for consultation and consensus management
Information	**Access to information** • Set up of a database with doctors specialised in area • Development of database of easy access to clinical trials and new treatments with easy accessibility for patients despite their site of residence
	Website • Website for doctors and patients • Website • Australian-specific website detailing the disease and treatment options for both physicians and patients is essential! • I would support the idea of a single website for patients and practitioners and involve TCCA as well as Cancer Australia • Australian website for patients and doctors
Research	• Separate NET trials group and not part of already established trials group • Clinical trials of treatments rather than individual outcomes • Agreed process for deciding on a national/international research agenda • More avenues for funding into research of the biology and natural history of NETs
Access to new technologies	• TGA approval of peptide radionuclide therapy • Make octreotide based diagnostic and therapeutic scanning available nationally • In Australia, incorporate new methods, eg 68-Gadolinium octreotide PET, 177-lu-octreotide treatment – not in US or EU guidelines • Availability of second line assays for tumour markers beyond CgA in Australia

Topic	Priority
Early detection	• Earlier diagnosis/therapy • Early diagnosis and management • Screening test
Special interest group	• Establish a NET interest group • A NETs interest group in Australia to lobby government, eg funding for new studies as well as treatment • National link between society/special interest groups/ENETs
Individualisation	• Management should be individualised to the requirements of individual patients beyond disease control and survival • Define individual tumour type
Service improvement	• Identification of pathway of advocacy – is it state health? Is it Federal?