Neuroendocrine Tumour Workshop 2009

Presented by Cancer Trials New Zealand (CTNZ)

1 May 2009

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Introduction

On 1 May 2009, Cancer Trials New Zealand convened the “Neuroendocrine Tumour Workshop 2009”, a one-day workshop held in the Auditorium, Auckland Hospital in Auckland, New Zealand.

The aims of the workshop were to:
- Provide information on state-of-the-art management of neuroendocrine tumours (NETs).
- Highlight critical points in diagnosis and management of NETs, to contribute to standardising care of patients with NETs in New Zealand.
- Agree a minimum level of care at local, regional and national levels in New Zealand.
- Develop an action plan for advancing the field of NET management in New Zealand.

In achieving the above, it was intended that the workshop would provide the basis for the development of guidelines for NET management in New Zealand.

The meeting was attended by 58 participants from a range of disciplines including gastroenterology, radiology, nuclear medicine, endocrinology, medical oncology, haematology, radiation oncology, surgery, internal medicine and pathology.

The workshop comprised a series of seven presentations, followed by a panel discussion. The workshop programme was as shown in Appendix 1.

This report presents a summary of the workshop, reviewing each presentation in turn and summarising the panel discussion.

Workshop introduction

Dr Mike Findlay, Medical Oncologist, Director, Cancer Trials New Zealand

Dr Mike Findlay opened the Neuroendocrine Tumour Workshop 2009, acknowledging the essential contribution to the meeting of the work of the convenors Dr Dragan Damianovich and Dr Amanda Ashley and the unrestricted educational grant from Novartis Oncology, New Zealand.

Dr Findlay highlighted the fit of the current symposium on NETs with the goals of Cancer Trials New Zealand (CTNZ). CTNZ has an interest in development of clinical trials research and translation of research from laboratory to clinic and from clinical trial to clinical practice. Part of the CTNZ brief is to hold such symposia on particularly interesting or more problematic cancers to contribute to progress in management of these cancers and, in turn, to possibly yield research opportunities.
Summary of workshop presentations

Seven presentations provided context for the panel discussion held in the second part of the workshop. An overview of each presentation is provided in this section.

Scope of the problem in New Zealand

*Dr Dragan Damianovich, Medical Oncologist, Auckland, New Zealand*

Dr Damianovich opened by reviewing the terminology changes that have applied to NET over the past century and defined NET as follows:

“rare group of heterogeneous neoplasms arising from the diffuse neuroendocrine system of the gastrointestinal tract or bronchopulmonary system”.

The term “neuroendocrine tumours” was introduced in the 1980s with the most recent update being the expansion of that term in 2007 to gastro-entero pancreatic neuroendocrine tumours (GEP-NETs).

Dr Damianovich noted that while 30% of NETs arise from the bronchopulmonary system, an area where much work is needed, this was not the topic of the current symposium. The majority of NETs arise from the gastrointestinal tract and there have been substantial shifts forward in their management in recent years. GEP-NET distribution is as follows:

- small intestine 38%
- rectum 20%
- appendix 17%
- colon 11%
- stomach 7%
- pancreas 7%.

Although NETs are perceived as rare tumours, their incidence (reported as 5–6/100,000 in the early 2000s) has significantly increased in the past ten years, by as much as 100% in the US and Europe. While the true cause of the rising incidence is unclear, the following possible contributing factors have been identified:

- increased NET awareness
- improvement in classification
- widespread use of endoscopy in cancer screening (particularly for rectal carcinoid)
- improvement in imaging
- changes in dietary habits
- environmental factors
- use of certain medications (including proton pump inhibitors).

Prevalence figures highlight that NETs are not that rare with 29-year limited-duration prevalence as follows (Yao et al 2004):

- NETs 103,312
- gastric 65,836
- pancreatic 32,353
- oesophagus 28,664
- hepatobiliary 21,427

Applying North American/western figures to New Zealand, the expected incidence in New Zealand is 250–350 cases/year (based on incidence of 6–8/100,000) with prevalence of 1000–1500/year.

Dr Damianovich went on to review the challenges presented by NETs, highlighting:

- variable clinical presentations with diagnosis often late in natural development
markedly variable clinical course and prognosis
requirement for prolonged monitoring
lack of standardised approach to the diagnosis and management which prompts interest in guideline development
limited high level of evidence on which to base recommendations
lack of access to multidisciplinary care in most centres worldwide
lack of improvement in outcomes.

Critically, he noted that there has been little funding for NET research. However, he highlighted that this unmet need has been recognised and the July 2007 NET summit in Bethesda, Maryland was a critical step forward that identified the following issues and recommendations.

Issues in NET management:
1. Limited understanding of cellular and molecular biology of neuroendocrine cells and mechanisms of tumorigenesis.
2. Shortage of in vitro and animal models to study disease pathogenesis and treatment.
3. Paucity of specific targets for new therapies.
4. Paucity of investigators in NET disease.
5. No uniform pathological classification or staging.
6. Lack of molecular prognostic factors to identify high risk patients and lack of understanding of natural history of these tumours.
7. Lack of understanding of disease complications that lead to morbidity and mortality.
8. Few centres which offer the multidisciplinary expertise required for the diagnosis, staging and management of GEP-NETs.

Recommendations for improved NET management:
1. Improve education of physicians and public in regard to early recognition of the symptoms of disease and the principles of management.
2. Develop tumour and plasma markers that can be used for early diagnosis and to monitor disease treatment.
3. Develop standardised pathology, incorporating methods for minimum pathological diagnosis and classification. Use the TNM [tumour, node, metastases] classification system for prognosis and coordinate classification systems with WHO and European criteria.
4. Establish regionalised centres of expertise that will expand the number of new investigators in the field and provide tumour banks with appropriate clinical and laboratory data.
5. Develop better imaging modalities.
6. Develop more effective treatments of advanced disease preferably from increased understanding of molecular pathogenesis and increased use of animal models and cell lines.
7. Facilitate trials of new agents and improve availability of promising agents.
8. Improve the molecular understanding of NETs through the application of genomic RNA interference, microRNA, proteomic, and small molecule screen technologies.
9. Improve understanding of the development of the diffuse neuroendocrine cell system, including enterochromaffin (EC) cells, to better understand the development of abnormalities in these cells.

Dr Damianovich closed by emphasising that the symposium’s goals, as set out in the workshop introduction, are directly along the lines of the above recommendations.
Pathology of NETs

Dr Mee Ling Yeong, Pathologist, Diagnostic Medlab, Auckland. New Zealand

Dr Mee Ling Yeong opened by highlighting that the battery of stains and molecular tests that can be applied to a particular NET to provide an indication of potential behaviour of these NETs are not necessarily always available to the pathologist. Typically, tumour diameter and extent of invasion are used alongside a number of stains with the aim of providing information of value to oncology colleagues.

Overview of the gastrointestinal-neuroendocrine system

Dr Yeong presented an overview of the gastrointestinal (GI)-neuroendocrine system (NES) locations and functions noting:

- The GI-NES is the largest endocrine system in the body.
- The endocrine cells differ from other endocrine organs, such as the thyroid, in that they are dispersed singly rather than forming organs.
- The cells lie adjacent to the epithelial cells of the GI tract with which they have a common origin.
- Collectively, GI-NES cells secrete about 30 hormones that regulate intestinal motility, digestion and take part in immune surveillance.
- They are called neuroendocrine cells because of the close interaction with the nerve cells of the GI tract and they have nerve-like endings.
- Some secretory peptides and amines found in NES cells are also found in the cells of the central nervous system as neurotransmitters and modulators.

Dr Yeong reviewed terminology emphasising the importance of discouraging the earlier term “carcinoid” because it tends to include all tumours in this group despite the differences in cellular origin, behaviour and prognosis. She highlighted that the term NET is now used, with special qualifiers in regard to site, size, and depth of invasion, which provide better insight into likely NET behaviour.

Origin of neuroendocrine tumours

NETs can arise in multipotential stem cells that give rise to all cells in the gastrointestinal mucosa. They may also arise in precursor neuroendocrine cells or from terminally differentiated neuroendocrine cells. Nearly all show some expression of cytokeratin and expression of CDX2, an intestinal transcription factor. This suggests that tumours arise in the epithelial precursor cell. The co-expression of epithelial markers is useful in determining the origin of a metastatic NET as NETs tend to co-express the epithelial markers of the region in which they arise. For example, bronchial NETs will co-express TTF1. NETs of the upper GI tract will express CK7 and NETs of the lower GI tract will express cytokeratin 20.

Pathology reporting of GI-NETs

Pathology reporting of GI-NETs has improved and become more standardised over the last several years.

Ideally reports will set out:

- site of tumour, given that NETs behave differently in different regions
- multiplicity if present (typically in 12%)
- size
- degree of differentiation
- depth of invasion/surgical margins
- proliferation indices
- surrounding disease; some NETs will arise in a background of chronic inflammation, eg, chronic gastritis or chronic inflammatory bowel disease (IBD)
- functioning or non-functioning status.

The WHO classification (refer table 1) is most commonly used and is easy to apply in a pathology laboratory.
Table 1: WHO classification for pure NETs

<table>
<thead>
<tr>
<th>Type and Grade</th>
<th>Behaviour</th>
<th>Explanatory notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade I</td>
<td>Benign</td>
<td>&lt;1cm, bland, non functioning, no angioinvasion, confined to mucosa/submucosa</td>
</tr>
<tr>
<td>Grade II</td>
<td>Uncertain malignant potential</td>
<td>Between 1-2cm, bland, non functioning, confined to mucosa/submucosa, may show angioinvasion</td>
</tr>
<tr>
<td>Grade III</td>
<td>Malignant, low grade (well differentiated)</td>
<td>&gt;2cm, functioning or non-functioning, deeper invasion (of muscle wall). All functioning, well differentiated tumours of ANY size.</td>
</tr>
<tr>
<td>Grade IV</td>
<td>Malignant, high grade (poorly differentiated, small cell carcinoma)</td>
<td>Uniformly poorly prognosis, functioning or non, called small cell carcinoma</td>
</tr>
</tbody>
</table>

Different grades as they apply to the different sites of the GI tract are as shown in table 2. Basic criteria as in Table 1 apply with a few exceptions, for example, cut off size between benign and malignant is larger for large intestine and appendix and there is invasion of mesoappendix in grade III disease in the appendix.

Table 2: WHO classification of gastrointestinal endocrine tumours

<table>
<thead>
<tr>
<th>Site</th>
<th>Well-differentiated endocrine tumour (benign behaviour)</th>
<th>Well-differentiated endocrine tumour (uncertain behaviour)</th>
<th>Well-differentiated endocrine carcinoma (low-grade malignant)</th>
<th>Poorly differentiated endocrine carcinoma (high-grade malignant)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stomach</td>
<td>Confined to mucosa-submucosa, ≤10 mm, no vascular invasion</td>
<td>Confined to mucosa-submucosa, &gt;10 mm or vascular invasion</td>
<td>Well to moderately differentiated. Invasion to muscular’s propia or beyond or metastases</td>
<td>Small cell carcinoma</td>
</tr>
<tr>
<td>Duodenum, upper jejunum</td>
<td>Confined to mucosa-submucosa, ≤10 mm, no vascular invasion</td>
<td>Confined to mucosa-submucosa, &gt;10 mm or vascular invasion</td>
<td>Well to moderately differentiated. Invasion to muscular’s propia or beyond or metastases</td>
<td>Small cell carcinoma</td>
</tr>
<tr>
<td>Ileum, colon, rectum</td>
<td>Confined to mucosa-submucosa, ≤10 mm (small intestine), ≤20 mm (large intestine), no vascular invasion</td>
<td>Confined to mucosa-submucosa, &gt;10 mm (small intestine), &gt;20 mm (large intestine) or vascular invasion</td>
<td>Well to moderately differentiated. Invasion to muscular’s propia or beyond or metastases</td>
<td>Small cell carcinoma</td>
</tr>
<tr>
<td>Appendix</td>
<td>Non-functioning, confined to appendiceal wall, ≤20 mm, no vascular invasion</td>
<td>Enteroglucagon-producing Confined to subserosa &gt;20 mm or vascular invasion</td>
<td>Well to moderately differentiated. Invasion to mesoappendix or beyond or metastases</td>
<td>Small cell carcinoma</td>
</tr>
</tbody>
</table>

With regard to metastatic rates, Dr Yeong presented data showing that small tumours (<1cm) in the small intestine can show metastases (circa 5%; despite classification under WHO as benign). By comparison, in appendix anything under 2cm does not metastasise. In rectum, a very small proportion of small tumours (<1cm) can show metastases.

Dr Yeong reviewed the following guidelines for determining proliferation fraction according to grade of tumour:
- Grade I (benign), II (uncertain malignant potential): <2%.
- Grade III (malignant, low grade): 2–15%.
- Grade IV: (Malignant, high grade): >15%.
Site specific NETs
Dr Yeong presented the following key points regarding site specific NETs.

Oesophageal NETs
Oesophageal NETs are the least common GI-NET and may be one of three types:
- Classic well differentiated, small (<10mm) Grade I NETs. However, small cell carcinoma of the oesophagus occurs and care must be taken to exclude origin in a bronchial primary.
- More common neuroendocrine carcinoma or small cell carcinoma with dismal prognosis.
- Combined tumours.

Gastric NETs
Dr Yeong reviewed the four types of gastric NETs (refer table 3), noting that Type IV has only recently been characterised and there are few published cases. Gastric NETs comprise circa 6% of GI tract NETs.

In Type II gastric NETs, gastrin comes from a G-cell NET arising in the duodenum or pancreas. Dr Yeong noted that an unusual feature in Type II gastric NETs is the phenomenon of one NET giving rise to another NET; the G-cell NETs are usually associated with a multiple endocrine neoplasia type I syndrome.

Table 3: WHO typing of gastric NETs

<table>
<thead>
<tr>
<th>Table 2. World Health Organization typing of ECL-cell gastric carcinoid tumours (modified after Abraham et al.)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-existing condition</td>
</tr>
<tr>
<td>Hypergastrinaemia</td>
</tr>
<tr>
<td>Carcinoid tumours</td>
</tr>
<tr>
<td>Distant (liver) metastasis</td>
</tr>
<tr>
<td>Outcome</td>
</tr>
<tr>
<td>ECL-cell hyperplasia/dysplasia</td>
</tr>
<tr>
<td>Background mucosa</td>
</tr>
<tr>
<td>Clinical management</td>
</tr>
</tbody>
</table>

*Postulated.
†Insufficient reported cases, but likely to be similar to type I.
MEN1, Multiple endocrine neoplasia type 1; ECL, enterochromaffin-like.

The mechanism for NETs that arise in chronic atrophic gastritis is believed to involve:
- Chronic atrophic gastritis with destruction of parietal cells producing intragastric hypoacidity which drives the antral G cells to produce increased levels of gastrin.
- Hypergastrinaemia which is a trophic hormone for the endocrine cells of the gastric body leading to corpus ECL cell hyperplasia, dysplasia and carcinoids.

Duodenal NETs
Duodenal NETs comprise 3% of GI tract NETs. Varieties are:
- gastrin secreting (G cells)
- somatostatin secreting (D cells) – these form gland like spaces and can be misdiagnosed as adenocarcinoma

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• serotonin/calcitonin secreting (may produce the carcinoid syndrome)
• gangliocytic paraganglioma
• poorly differentiated neuroendocrine carcinoma (ie, component of small cell carcinoma).

Small intestinal NETs
Small intestinal NETs, which comprise 30% of GI tract NETs, have features as follows:
• more common from proximal to distal
• may be multiple
• may secrete serotonin or substance P
• usually considered to be grade II tumours at least including small tumours because of propensity to metastasise
• may be associated with carcinoid syndrome
• most are >20 mm.

Large intestinal NETs
Large intestinal NETs are of two different types:
1. Colonic NETs which comprise <10% of GI tract NETs. Two-thirds of these NETSs arise in the caecum and right colon. They are the most aggressive form of GI NETs and have features as follows:
   • usually bulky growths at diagnosis
   • usually metastases present
   • carcinoid syndrome in about 5%
   • all colonic NETs, other than those in rectosigmoid and appendix, should be regarded as potentially malignant
   • a small cell variant exists, and in about 50% of patients arises in association with an overlying adenoma or adenocarcinoma.
   • prognosis is dismal.
2. Rectal NETs which comprise 17% of GI tract NETs and have features as follows:
   • usually arise in the midportion of the rectum
   • usually small, polyps covered by normal mucosa
   • usually benign small lesions
   • a few are larger; those >20 mm invade the wall and may metastasise.

Dr Yeong highlighted that CgA is not present in NETs of the distal large intestine but present more proximally, reinforcing the need to use a panel of stains, typically CgA, synaptophysin and CD56 which in practice will cover most NETs.

Appendiceal NETs
Appendiceal NETs are the most common GI-NET comprising 33% of GI tract NETs. Features are as follows:
• usually small, 1cm or less, discovered incidentally
• lymph node metastases in 4%, usually in tumours >20 mm
• distant metastases in 1%, larger tumours with deeper invasion, ie, to serosa and mesoappendix
• local treatment adequate except for the larger lesions or those with serosal invasion where right hemicolectomy may be appropriate
• rarely, present with carcinoid syndrome.

Appendiceal NETs with mucin secretion are believed to be true hybrid tumours with combined glandular and NET features, although sometimes the latter is not markedly expressed. They are called goblet cell carcinoid, adenocarcinoid, crypt cell carcinoid, or mucinous carcinoid. The malignant version behaves as an adenocarcinoma and in metastatic form it is very hard to locate the neuroendocrine characteristics.

Pancreatic NETs
Pancreatic NETs are classified into:
- Functional (syndromic) which account for 65–75% and include insulinoma, glucagonoma, gastrinoma, somatostatinoma, VIPoma. Most are potentially malignant although most insulinomas are quite indolent.
- Non-functional (non-syndromic).

The pathological classification of pancreatic NETs is as follows:
- Pancreatic endocrine microadenoma: less than 5 mm, discovered incidentally, benign.
- Differentiated NETs which account for the majority of pancreatic NETs.
- High grade NET carcinomas – small cell carcinomas.

A small group of pancreatic NETs present as cystic lesions and should be considered in the differential diagnosis of cystic lesions of the pancreas.

The following are key points regarding prognosis in pancreatic NETs:
- Microadenomas behave in a benign manner.
- Insulinomas generally show an indolent course.
- Other functional tumours recur or metastasise in 50–70% cases.
- Tumours <20 mm are generally low risk.
- Other prognostic factors are necrosis, mitotic rate, vascular invasion and extrapancreatic invasion.

Summary
Dr Yeong summarised by reiterating the following regarding NETs:
- NETs of the GI tract and pancreas form the largest proportion of NETs in the body (70%).
- They may be functioning or non-functioning.
- They exhibit a range of behaviours which depend on the site, cell of origin, size, differentiation, depth of invasion and presence or absence of angioinvasion and associated disease. These features should be recorded in the pathology report.
- They may be associated with inherited disorders such as multiple endocrine neoplasia type 1 (MEN1) or neurofibromatosis type 1 (NF1) which applies to duodenal somatostatinomas.
- Grading uses the WHO classification of I benign, II uncertain malignant potential, III well differentiated malignant and IV poorly differentiated malignant.

The rapid pace of slow progress: recent advances in NET disease
Professor Irvin Modlin, Surgical Oncologist, Yale University School of Medicine, New Haven, Connecticut, US

Introduction
Professor Modlin opened by briefly touching on the status with NET at the outset of his involvement in 1975. At that stage, management was limited by the tools available to identify lesions and little therapy outside surgery was available.

He acknowledged the confluence of thought leaders at the time, for example, in the areas of peptide hormones and cytochemistry, and the resulting paradigm shift in NET management that occurred in the 1980s.

In an overview of thinking regarding NETs over the 20th century, Professor Modlin noted that:
- Oberndorfer’s 1907 recognition of NET as carcinoid or “cancer-like” was correct in distinguishing NET as a different tumour but erroneous in identifying NETs as benign lesions.
- The prolonged confusion caused by the above was added to by Pearse’s conclusion (1969) that NETs were all derived from a common cell system, despite there being some value in this framework for thinking. Thus, it was appropriate to put aside the concept of APUDomas (amine precursor uptake and decarboxylation).
Feyrter in the 1930s was correct in recognising a family of endocrine cells that are all part of a diffuse neuroendocrine system from which “similar” tumours arise at different sites.

In relation to the latter point, Professor Modlin described differentiation of treatment on the basis of functioning versus non-functioning tumour as “archaic and incorrect”. All tumours are NETs and all should be treated the same way. He noted that this was recognised by Feyrter but that this early prescient thinking was obscured by the interruption of the Second World War and the loss of many of the thought leaders and centres of excellence in Germany and Austria.

**Moving on from “locoregional” treatment**

Professor Modlin strongly emphasised the need to put aside the idea of “locoregional disease” and to introduce a different way of thinking about NET disease. He highlighted the importance of recognising that the vast majority of NET disease is systemic not “regional”.

> “[NET] can be a virulent and aggressive cancer and we are challenged to establish which NETs are “bad players.”

There is a requirement for pathologists and molecular biologists to identify specific grades of tumour and, thus, differentiate NET disease in order to highlight important windows of therapeutic opportunity.

The latter requirement also highlights a critical aspect of effective NET management: the need for a multidisciplinary team with members who understand different aspects of the disease. The use of multiple specialties conferring regarding individual patients in order to determine a way forward challenges the traditional, intellectual hegemony of medicine where one “expert” dictates treatment and/or leads thinking.

> “There is no one individual of intellectual predominance when it comes to neuroendocrine tumour treatment."

Professor Modlin presented survival rates for GI-NETs, describing these as relatively good for localised disease (57–91% 5-year survival rates) and, by comparison, very poor for distant disease (10–40% 5-year survival rates). The spread in outcome rate reflects the current inability of pathology to clearly identify tumours with a highly malignant phenotype and the fact that a localised lesion may exhibit a high grade histology albeit a low stage (ie, local).

Although rates of survival for regional disease are reported, Professor Modlin reemphasised that this is an arbitrary classification given that regional disease is, effectively, advanced disease. Thirty percent of excisions occur in localised disease (most are appendiceal, gastric or rectal) and 60% in advanced disease (comprises regional and distant). Unsurprisingly, there is a dramatic fall off in overall 5-year survival rates between localised and advanced disease (refer figure 1). If these data are combined with histological grading, the outcome is significantly different, but unfortunately in the SEER database, 60–70 % of lesions have not been graded.

Professor Modlin also noted that while five-year survival rates appear to be good, they are poor if one considers that many of these patients should be able to live 15–20 years; a focus on five-year survival for patients with pancreatic, gastric or oesophageal adenocarcinomas has unreasonably lowered the bar for NET and this needs reconsideration.

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1 SEER (Surveillance, Epidemiology and End Results) collects information on incidence, survival, and prevalence from specific geographic areas representing 26 percent of the US population and compiles reports on all of these plus cancer mortality for the entire US.
As the vast majority of disease will be regional, this will predictably be associated with distant or metastatic disease. The fact that it is often not detectable, using current strategies, results in significant incorrect downstaging. On that basis, surgery alone is likely to be ineffective since there is no adequate means to detect residual disease in terms of micrometastatic disease or disease in lymph channels.

Equally, the liver remains the primary and dominant issue in NET and for practical purposes the primary therapeutic target is macro- and microhepatic metastases.

Fibrosis also must be considered; fibrotic tissue provides the “gasoline” that drives NE cells to proliferate. There is need to consider both the cancer cells and the milieu within which these cancer cells grow. The growth factors that make NET cells proliferate come to a large extent from the micro milieu and, particularly, from the fibroblasts. Targeting cancer cells without addressing the micro milieu is destined to fail.

Addressing fibrosis and its effects is critical; fibrosis causes a substantial number of issues in numerous sites, especially where there is improved longevity. The longer tumour secretion of bioactive products continues, the more likely there will be local peritoneal fibrosis (bowel obstruction) and right-sided cardiac valvular disease.

In consideration of what may be needed to advance management of NET's, Professor Modlin highlighted:
- Surgery is effectively as “good as it can get” and bigger/better surgery is not likely to be key.
- Earlier diagnosis is relevant but is proving challenging. In terms of unmet needs, this probably remains the key issue
- Novel therapeutic strategies are likely to be important.

The current approach of removing visible tumour and achieving clear pathology reports, and then waiting for metastatic disease to appear means effectively missing a four- to five-year therapeutic window during which proliferating residual cells or micrometastases could have been switched off by use of an appropriate targeted antiproliferative therapy.

Professor Modlin went on to describe an alternative approach involving a series of marker genes, used to identify residual disease. By identifying marker genes that regulate apoptosis, proliferation and metabolism, particularly in the Wnt signalling pathway, it is possible to have a series of markers that can be found in tissue or plasma and used to predict residual disease.
A summation of considerable work in this area has identified:

- **MAGE-D2**: melanoma antigen D2
- **MTA1**: metastasis-associated protein 1
- **NAP1L1**: nucleosome assembly protein 1-like
- **Ki-67**: proliferation-related Ki-67 antigen
- **Survivin**: apoptosis inhibitor
- **FZD7**: Receptor for Wnt proteins
- **CgA**: parathyroid secretory protein 1
- **Kiss1**: metastasis-suppressor protein
- **NRP2**: vascular endothelial growth factor-165.

This approach offers detection using transcript expression in tissue and plasma as opposed to purely tumour size and histology to achieve a “likely” prognosis. Using a mathematical tool (principal component analysis) it is possible to effectively distinguish different tumours, metastases and normal tissue (refer figure 2). The separation between tissue types shown in figure 2 is indicative of distinct gene-level profile and confirms that the identified panel of genes can be used further to distinguish normal mucosa, primary small intestine NETs and metastatic small intestine NETs.

**Figure 2: Principal component analysis using 26 differentially expressed genes distinguishing normal mucosa, primary small intestine NETs, and metastatic small intestine NETs**

Consideration of marker genes from the perspective of tissue tumour burden and WHO pathological classification shows metastases have substantially different gene expression to localised tumours. This means the ability to detect which tumours have different gene expression and will enable a determination of whether a localised tumour exhibits genes that predict metastatic behaviour or whether residual disease remains where a tumour had been considered to have been completely resected, based upon the continuing identification of elevated plasma transcripts.

Such an approach underpins the original proposition that there is no “locoregional disease”. Almost all NET disease except appendiceal or gastric NETs is systemic and the focus should be on how to treat disease once tissue or plasma transcript abnormalities indicative of a malignant/metastatic phenotype have been identified.

**Therapeutic options in NETs**

Professor Modlin summarised the following therapeutic background points:

- The majority of patients present with metastatic disease (>60–80 %) making “locoregional treatment” redundant.
- Unique expression of peptide hormone receptors, mainly somatostatin receptors (SSRs) provides good targets for therapy.
Tumour growth is often slow, providing opportunities to try different treatment modalities. It is necessary, however, to establish which tumours are faster growing. Ki-67 and mitotic indices are available but molecular diagnostic markers/transcripts are required for tumours of smaller sizes (e.g., <1mm).

Life-threatening symptoms can be present (carcinoid crisis, Verner Morrison syndrome).

Therapeutic options in NETs are:

- Surgery which is very often ablative and rarely curative.
- Debulking: radiofrequency ablation (RFA); embolisation/chemoembolisation/radioembolisation (Spherex®).
- Medical therapy: chemotherapy, biological treatment (somatostatin analogues [SSAs], interferon-alpha, m-TOR inhibitors, VEGF [vascular endothelial growth factor] receptor inhibitors, other TKIs [tyrosine kinase inhibitors]).
- Irradiation: external (bone, brain-metastases), tumour targeted, radioactive therapy (MIBG [metaiodobenzylguanidine], 90Y-DOTATOC, 177Lu-DOTATATE).

The treatment of most patients is a combination of surgery, PRRT [peptide receptor radionuclide therapy] and medical treatment.

Professor Modlin reviewed the following factors influencing the therapeutic decision emphasising that a tumour’s functioning or non-functioning status is NOT regarded to be relevant to the treatment decision:

- Type of NET tumour.
- TNM [tumour, node, metastases] stage and grade.
- Extent of liver involvement.
- Patient’s performance status; how the patient will handle therapy.
- Availability of different therapeutic modalities.

Biochemical confirmation, currently using CgA in plasma until reviewed with molecular markers, and topographic localisation are also used.

Professor Modlin then presented a therapeutic strategy for “locoregional/systemic disease”. He noted that the majority (80–90%) of patients are multiple and metastatic at diagnosis and the liver is the final target. This can be described as treating the “rear end of the disease” which is not ideal but reflects current status with management.

Professor Modlin presented the simplistic therapeutic algorithm for NETs in figure 3 with the following notes:

- Decisions must be taken on a patient-by-patient basis.
- Surgery needs to be performed by experts.
- En bloc resection and lymphatic drainage are standard.
- If there are no metastases, the patient is in a good position but there is no way to be certain of this. If one assumes there are metastases, as there will be in most patients, the strategy as shown is proposed.
- It is inevitable that there will be debate regarding choice from the treatment options for overt evident liver metastases/residual disease. Choice will, to some extent, be driven by available expertise. The critical requirement is to try to get the liver tumour burden to under 10%; there are clear data that there is a series of agents which are very effective at obliterating residual tumour disease in that situation.
Management of liver

Typically, because there is no surveillance test, a NET primary is found late (unless the tumour has caused bleeding, obstruction or perforation of intestine) and about 80% of patients have metastatic disease. At that point, the lymph nodes and mesentery are a major issue to address. Beyond that, hepatic metastases need to be addressed. These are both visible metastases, which are possibly respectable, usually largely based on surgeon expertise, and micrometastases.

On investigation, about 80% of livers believed to be free of metastatic disease are positive on needle biopsy and reverse transcription polymerase chain reaction (RT-PCR) analysis of transcripts for NE disease, ie, even liver that appeared normal has an approximately 80% chance of having micrometastases of NET.

Undetectable metastases are an issue without specific markers in plasma to pick them up; current research tools for this should be available in next 18 to 24 months.

In summary, the current situation, for NET management is:

- classic en bloc resection with regional lymph node extirpation
- no technique available to demonstrate residual disease
- 60–80% of pathologically negative lymph nodes (on CgA or synaptophysin staining) are positive on RT-PCR for NET transcripts.

Achieving 10% liver burden provides a therapeutically optimal window. The various management strategies include:

- surgery
- cytoreduction
- hepatic transplantation
- chemoembolisation
- chemotherapy
- biotherapy
- symptomatic management.
Apart from transplantation, each of these procedures can achieve equally good results (expert and institution dependent).

Professor Modlin presented the following data on the effectiveness of these procedures:
- Uppsala data show a major survival advantage from resecting the primary in midgut carcinoids (figure 4), overturning the view that, where the liver is “full of tumour”, the primary should be left. It is now recognised that removing the primary is of value as it really reduces tumour volume.
- Equally eliminating liver metastases is typically hugely advantageous (figure 5).
- Evidence for removing the primary is fairly limited; the best data are in gastrinoma where removal of the primary and hepatic metastases, as much as possible, results in a marked difference in survival rates (figure 6).

There can be extended debate about the degree of expertise required and how extensively disease should be removed; at a simple level, the more tumour removed, the better patients will do, especially now that there is effective therapy to deal with residual disease.

*Figure 4: Cumulative survival of patients with and without primary tumour resected (midgut carcinoids) P Hellman et al. World J Surg 2002; 991*

*Figure 5: Cumulative survival of patients with and without liver metastases (midgut carcinoids) P Hellman et al. World J Surg 2002; 991*
Locoregional management is dependent on cell type

Professor Modlin described a future where pathologists identify the cell biology, ie, what NE cell it is, immediately clarifying features such as growth rate.

He highlighted that, ultimately, major ablative surgery will not be needed once there are pharmacotheapeutically targeted probes to addresses the disease process for different NETs.

He further described this using the example of gastrinoma and gastric NETs.

Recognition that the key issue was not the tumour but hormone produced by tumour, ie, that gastrin was driving the disease, led to recognition that NE disease it is a cell disease that is NET based. In the case of gastrinoma and gastric NETs:

- parietal cells secrete protons
- protons switch on or off the gastrin cells
- gastrin cell drives the histamine producing ECL cell, generating histamine
- once there is a tumour, there is G cell/gastrin driven hyperplasia of E cells, parietal cells, ulceration and tumours either in pancreas or fundus.

NETs of the stomach were then recognised as a series of different varieties including:

- Gastric NETs of fundus driven by hypergastrinaemia related only to atrophic gastritis which can be ignored for practical purposes. These are enterochromaffin-like (ECL) tumours and they do not proliferate to the stage where they invade or metastasise about 98% of time.
• Type II which is also ECL-cell but much more dangerous; the background is a menin 1 lesion, part of multiple endocrine neoplasia type 1 (MEN1). Twenty to 30% invade, become aggressive and metastasise.
• Type III mixture of cells in stomach, mostly EC, which behaves very aggressively like adenocarcinoma.

This understanding of different cell types and cell types driven with different genes markedly changes what locoregional therapy might be.

This has meant a major shift from total gastrectomy and total pancreatectomy down to local resection of small duodenal lesions with endoscopes or local duodenal resections and a series of pharma-therapeutically-targeted probes (proton pump inhibitors, cholecystokinin-B (CCK-B) receptor antagonists, octreotide LAR[long acting release], lutetium radioisotope therapy) to control the disease process, with most people living for 10–15 years.

In a situation where there is a pancreatic tumour producing gastrin, major ablative surgery is not required as there is a targeted treatment to addresses the disease process.

The advances seen in gastrinoma are predicted for NETs of other parts of the bowel as more is determined about cellular biology.

Different types of hepatic metastases can be treated by various modalities:
• excision
• embolisation; there are limited data on chemoembolisation but indications of reasonable objective responses for reasonably non-invasive process
• cytotoxics
• radiofrequency ablation: this is reasonably effective where lesions are not too big and provides an effective mode of therapy for locoregional ablation, especially now that the need to get to under10% tumour burden is understood.
• transplantation.

Critically, there are clear data showing that the more metastatic tissue removed, the better the survival outcome.

Once the 10% local regional tumour burden is reached, options are:
• chemotherapy:
  • local (chemoembolisation)
  • systemic
• biotherapy:
  • SSAs: particularly effective as directed against the 2 and 5 receptors. It is also possible to use an SSR profile to determine pathologically when agents will be effective on residual disease
  • interferon-alpha
  • VEGF-inhibitors: bevacizumab, sunitinib
  • m-TOR inhibitors
  • others.

Generally accepted indications for SSA therapy include:
• peptide/amine induced syndromes with clinical symptoms; SSAs known to switch off symptoms
• progressive or metastatic disease
• antiproliferative: now have PROMID2 evidence of a massive difference in time to tumour progression with octreotide LAR vs placebo (refer figure 7), most marked in patients with tumour load under 10% (refer figure 8) and irrespective of whether the tumour is functioning or not functioning.

2 Placebo-controlled prospective randomised study on the antiproliferative efficacy of Octreotide LAR in patients with metastatic neuroendocrine mid gut tumours.
Perioperative use to prevent “carcinoid crisis”:
- in patients whose symptoms are well controlled with octreotide LAR a supplemental dose of IR octreotide sc or iv (50–200 μg) can be given 1–2 hours prior to the procedure
- emergency surgery: Octreotide 500–1000 μg iv/bolus or IR octreotide 500 μg sc 1–2 hrs pre-procedure followed by continuous iv infusion octreotide 50–200 μg/hr.

Figure 7: Time to tumour progression with octreotide LAR versus placebo. Arnold R. ASCO GI 2009 Abs#121

Figure 8: Time to tumour progression with octreotide LAR versus placebo by tumour volume. Arnold R. ASCO GI 2009 Abs#121
Radionuclide imaging and therapy for neuroendocrine malignancy
Dr Kate Moodie, Radiologist and Nuclear Medicine Specialist, The Peter MacCallum Cancer Institute, Melbourne, Victoria, Australia

Introduction
Dr Moodie opened by illustrating the value of 68-gallium (68Ga)-labelled octreotate for positron emission tomography (PET) imaging with a very recent case of a patient with what was thought to have been the primary NET previously resected from the second part of duodenum. Further management had been sought to address continued troubling symptoms. In disease staging, multiphase computed tomography (CT), magnetic resonance imaging (MRI) with contrast multiphase and 111-indium(111In)-labelled octreotide single photon emission computed tomography (SPECT)/CT all showed no abnormality. In contrast the use of 68Ga DOTATATE PET/CT imaging showed abnormal uptake in the tail of pancreas and very clearly indicated a lesion that was likely to be the primary.

Conventional imaging
Coverage of conventional imaging was intentionally restricted in the presentation but Dr Moodie highlighted that attention to detail is critical in neuroendocrine disease. With CT and MR, multiphase imaging is imperative as tumours, certainly in the liver, are known to be variably visible on the different phases of contrast. Standard imaging should be pre-contrast, arterial phase and portal venous phase. In areas such as the pancreas, finer slice imaging is needed to maximise chances of finding lesions.

Octreotide scintigraphy
The following key points were made with respect to somatostatin receptor scintigraphy using radiolabelled octreotide (OctreoScan):

- The value of octreotide scintigraphy over conventional imaging is based on well-documented superiority over conventional imaging with respect to sensitivity, the ability to undertake whole body imaging without the sensitivity issues of whole body MRI and the lack of significant injection side effects. Octreotide scintigraphy provides prognostic information and facilitates treatment selection, and is known to change management in 20–30% of cases.

- Octreotide is a close analogue of somatostatin. The target is somatostatin receptor (SSR)-2, which is the receptor most commonly expressed in NET. 111In-labelled octreotide has high affinity for SSR-2 and SSR-5.

- Physical half-life of 111In-labelled octreotide (2.8 days) and gamma emission are suitable for delayed planar and SPECT imaging. Delayed imaging becomes important for differentiating normal uptake from disease, eg, in bowel.

- The 5-point “Krenning” scale is used for measuring intensity of tumour uptake, ranging 0 (no uptake) though grade 4 (intense) uptake. The scale uses uptake relative to normal distribution to assign grade.

- Indications for use are:
  - Diagnostic: for failed or equivocal biopsy and for localisation of primary.
  - Lesion characterisation: assessment of SSR density allows assessment of suitability for long-acting somatostatin analogue (SSA) therapy or peptide receptor radionuclide therapy.
  - Staging: either for pre-resection or for follow-up in advanced disease.

- The value of octreotide scintigraphy is reiterated in National Comprehensive Cancer Network (NCCN) guidelines for NET diagnosis which include octreotide imaging for localisation studies.

- The effectiveness of octreotide scintigraphy in diagnosis varies with tumour type: very high for mid gut carcinoid, gastrinoma and glucagonoma (75–100%), less sensitive for insulinoma (40–50%) and
low to variable for poorly differentiated NET.

- The octreotide scan result is used to predict outcome to SSA treatment. Of patients with a positive octreotide scan, 80% will respond to SSA treatment, and recent results of the PROMID study have indicated that use of long-acting octreotide may have a role in suppressing tumour progression in such patients. A negative scan tends to indicate suitability for chemotherapy, however, the negative scan may result from low receptor density and, thus, a trial of SSA may still be appropriate if the patient is symptomatic.

The advantages of SPECT over planar imaging and SPECT/CT over SPECT were presented using gallbladder uptake in a case as shown in figure 1. Hepatobiliary excretion leads to gallbladder visualisation in some patients. With planar imaging, it is very difficult to confirm normal excretion in gall bladder versus metastasis within liver.

SPECT/CT allows better localisation and avoids false-positive results; as such, it is becoming a very standard approach.

Advantages were also demonstrated with the case in figure 2 in a patient with a very enlarged liver, extending into left upper quadrant. SPECT/CT allowed clear differentiation of a liver metastasis versus peritoneal deposit.

*Figure 1: Normal distribution in gall bladder (indicated with red arrows) shown with SPECT imaging (top), CT (middle) and fused SPECT/CT images (bottom)*

PET imaging in NE disease

- The only tracer being in New Zealand for PET is 18-fluorine (\(^{18}\)F)-fluorodeoxyglucose (FDG). FDG – PET has little role in NE imaging unless used in combination with other tracers (refer below). This is confirmed in the NCCN guidelines on initial workup of NET.

- High tumour FDG-avidity on PET scan correlates negatively with somatostatin receptor expression and correlates positively with high Ki67 staining and poorer prognosis. FDG-avidity can be used to predict expected response to small cell lung cancer type chemotherapy regimens like carboplatin/etoposide. FDG-PET can be useful for therapeutic monitoring, giving an indication of activity where there is poorly differentiated disease. In the absence of significant uptake, FDG-PET is of limited utility unless new lesions develop that are negative on \(^{111}\)In-radiolabeled octreotide imaging. In this setting, FDG-PET allows demonstration of development or progression of poorly differentiated clones.

- \(^{68}\)Ga Octreotate PET using \(^{68}\)Ga linked to an SSA (\(^{68}\)Ga-DOTATOC and \(^{68}\)Ga-DOTATATE) is at forefront of diagnostic evaluation. Gallium has a workable half-life of 67 min and the procedure has the advantage that patients do not need to fast.
• Literature clearly demonstrates that gallium imaging, both DOTATATE and DOTATOC, is far superior for lesion localisation than standard indium octreotide scintigraphy with at least 30% more lesions being identified than on $^{111}$In-radiolabeled octreotide planar imaging.

• Expression of SSA receptors in gallium study and no uptake on FDG is a useful prognostic indicator for response to peptide receptor radionuclide therapy. A lack of sites with FDG without SSR makes PRRT feasible.

**PRRT: peptide receptor radionuclide therapy**

• PRRT has been used at Peter MacCallum Cancer Institute using various radiolabelled octreotide analogues alone and in combination with chemotherapy:
  - $^{111}$In-radiolabeled octreotide (ultra-short-range auger radiation): 1996-9 alone and 1999-2000 in combination with 5FU [5-fluorouracil].
  - 90-Yttrium ($^{90}$Y)-radiolabelled octreotide (long-range beta radiation): 1999-2000 as part of an international multicentre trial.
  - LuTate – 77-Lutetium ($^{77}$Lu)-lutetium (short-range beta and gamma emitter with greater affinity for SSR type 2): 2005-6 alone and 2006-present in combination with 5FU.
  - Efficacy of 5FU is used in combination with radionuclide therapy for its established effects in preventing DNA repair and its action as a radiosensitising agent. It is also inexpensive with a low-toxicity profile.

• Combination high-dose octreotide with 5FU may enhance treatment efficacy in NET. This novel approach which has not previously been reported in NET has been validated in cell culture.

• Haematological toxicity is a minor issue with LuTate and is seldom of clinical concern. Literature indicates no correlation between haematological toxicity and age, dose of LuTate dose, number of previous $^{111}$In-octreotide therapies, and use of 5FU chemotherapy. However, there is more marked depression of white cell and platelet counts in patients with scan evidence of bone disease, particularly with diffuse marrow infiltration. Treatment with $^{111}$In-octreotide is preferred in such patients.

**Close**

Dr Moodie made the following concluding points:

• There has been progressive improvement in symptomatic and scintigraphic response with no significant incremental toxicity with newer radionuclide therapy protocols.

• Cg-A provides a useful marker of therapeutic response; it is an important part of surveillance protocols.

• Combination treatment with chemotherapy is well tolerated and seems to increase efficacy.

• A multi-disciplinary approach to NET management is vital.

• New tracers and combination with novel agents likely to further improve outcomes

• There are opportunities for translational research using appropriate animal models.

**Selective internal radiation therapy for NET liver metastases. A new and effective modality for treatment**

*Professor Richard S Stubbs, Gastrointestinal Surgeon, Wakefield Hospital, Wellington, New Zealand*

Professor Stubbs opened by expressing a view that it is regrettable that selective internal radiation therapy (SIRT) and yttrium microspheres have not gained the attention that is possibly deserved and that he and others have recognised that this modality might have real value in neuroendocrine (NE) liver metastases.

**Current options for managing NET liver metastases**

Current options for managing neuroendocrine tumour (NET) liver metastases as follows deliver median survival of approximately 38 months. Professor Stubbs highlighted that none has been “wonderful”:
• Bland arterial embolisation
• Chemoembolisation
• Palliative liver resection ± ablation
• Ablative therapies, eg, radio frequency ablation/cryotherapy
• Chemotherapy: doxorubicin plus streptozotocin, interferon-alpha
• Octreotide therapy – for symptoms.

The SIRT modality
Professor Stubbs presented the following key points on the SIRT treatment modality:

• SIRT employs delivery into the hepatic artery of microspheres (25–35 μm in diameter) which are loaded with a high dose of the beta-radiation emitter yttrium-90. Because of their size, microspheres are trapped in the arterial end of the capillary bed.

• The basis of treatment is that all liver tumours, regardless of apparent vascularity, have a blood supply which is predominantly provided by the hepatic artery versus the portal vein. Spheres are effectively selectively delivered to tumours which get circa 90–95% of their blood supply from the hepatic artery compared with 25% in normal liver.

• Typical treatment delivers 1.5–3 GBq of yttrium-90 microspheres to the liver. The effective and absorbed dose of radiation will give an average dose to liver tumours of approximately 150–250 gray (Gy), an enormous dose compared with what is normally used clinically. Normal liver gets an average dose of approximately 20 Gy, lower than the level for significant liver injury. Thus, microspheres provide a convenient method to deliver doses of radiation that could not be delivered by conventional techniques.

Potential problems with SIRT
Professor Stubbs went on to provide the following key points regarding potential problems with SIRT:

• Radiation hepatitis: whole liver radiation in excess of 30–35Gy causes issues that will typically lead to progressive liver failure. This is a theoretical risk and in practice is almost never seen (estimated 1% incidence based on experience).

• Radiation pneumonitis: this has the potential to occur where microspheres slip through hepatic circulation through shunting and are trapped in lungs (ie, the “next” capillary bed). This risk is managed by modelling with technetium-labelled macroaggregated albumin (MAA) which is approximately the same size as microspheres to show sphere distribution. It is known that if <12% of MAA goes to the lungs, the lungs will not receive a damaging dose of yttrium.

• In contrast, radiation to foregut structures is a bigger problem that results from microsphere delivery through various hepatic artery branches including right gastric artery, gastroduodenal branch, and sometimes small branches to pancreas, duodenum or stomach. Only a few microspheres will result in severe gastritis, pancreatitis, or duodenitis.

• Radiation hepatitis and pneumonitis are not regarded to be a problem with careful administration. Radiation to foregut structures is the biggest concern with this modality and it is essential that delivery ensures microspheres are only going to liver. This risk is not identifiable on MAA scan unless very gross. The outcome is very serious, for example a radiation dose to stomach, and particularly the antrum where the spheres end up, results in serious radiation gastritis which may not heal in the lifetime of the patient.

Professor Stubbs also noted that the yttrium-90 dose impacts negatively on patients’ energy levels, as does the surgery.
Microsphere delivery
Professor Stubbs’ experience in colorectal cancer and the use of hepatic artery chemotherapy has meant a pattern of delivering yttrium therapy through a surgically placed port. In his view, this has been fortuitously useful; the use of methylene blue to test distribution after a port is placed surgically into the hepatic artery makes it possible to totally isolate the liver and very much reduce the possibility of inadvertent delivery.

Professor Stubbs recognises that this is not the standard approach but believes it is much safer to give yttrium therapy via a properly placed hepatic artery port than via percutaneous femoral catheter, especially if treating the whole liver. He noted that incidence of peptic ulceration with use of ports for yttrium is less than 5%, usually with minor effect, compared with >10% peptic ulceration from femoral catheter delivery with 50% of affected patients crippled with symptoms, potentially for their lifetime.

Thus, Professor Stubbs uses ports although not exclusively, and treats with hepatic artery chemotherapy (5FU[5-fluorouracil] 1.0g X 4 days every 4 weeks) when the port is being used. 5FU has a radiosensitisation advantage for the first cycle and provides an easy, inexpensive treatment which has been shown to have some activity against NET.

Experience with SIRT
Data were presented on 10 patients with NET treated in the last 10 years. Results have been very positive with:

- 8/8 of those with carcinoid symptoms showing symptomatic response, often for prolonged periods (resolution for 2–5 years versus 3–6 months).
- 4/4 with 5-hydroxyindolacetic acid (5H1AA) showing a 5H1AA response.
- 10/10 showing CT response on first SIRT.
- 3/3 showing CT response on second SIRT.
- Mean survival of 36.6 (11.9–84.5) months.

Professor Stubbs cited other reports in literature, noting that all those using this modality in NET have similar findings although not quite as effective possibly because the modality has been used differently. He acknowledged that data quality is imperfect but highlighted value in using available evidence.

Conclusion
It was concluded that:

- The SIRT modality delivers a very high response rate and excellent control of carcinoid symptoms.
- Delivery via a surgical port is preferred and believed to be safer.
- SIRT is ideal for liver-only or liver-predominant disease and that it should be considered as first-line therapy for those presenting with major hepatic disease.

NETs: Systemic treatment options
Dr Yu Jo Chua, Medical Oncologist, The Canberra Hospital, Canberra, Australia

Dr Chua opened by highlighting that the time is right to mobilise and improve management of patients with neuroendocrine tumours (NETs) and that his presentation takes the perspective of someone playing a role in facilitating this, rather than that of an expert in this area.

Dr Chua emphasised the importance of a multidisciplinary approach to NET management, noting that, while treatment schema and pathways are of value, the key is a group of people working together to assess each case individually. Equally there is a need for someone to coordinate the multidisciplinary management effort and for effort to direct patients into available clinical trials, although the latter may be quite limited. Dr Chua also noted that medical oncology focus is on evidence-based treatment and randomised, controlled trials but that randomised trials data in NETs are limited. He proposed a pragmatic approach would make the best of what data are available.
In reviewing the traditional paradigm for NET management, Dr Chua noted that there is modest anti-tumour efficacy from systemic therapies, particularly chemotherapy, and typically, where appropriate, locoregional or targeted approaches are preferred. Additionally, for somatostatin analogues (SSAs) which have typically been considered for the management of carcinoid syndrome symptoms, there is now emerging data suggesting that these agents may have antiproliferative activity and may, thus, slow tumour growth.

Emerging systemic therapies, including cytotoxic chemotherapy and targeted (biologic) therapies, are indicating an increasing role for medical oncologists, both in their administration and management of significant treatment related toxicities.

Dr Chua reviewed the following considerations in patient selection for chemotherapy:

- Histology: poorly versus well differentiated; to some extent, this can be a surrogate for biologic aggressiveness.
- Tumour grade: there is a push towards more objective tumour grading methods such as Ki67 and mitotic index.
- Extent of disease, tumour effects (uncontrolled carcinoid symptoms, mass effect) and rate of disease progression and other clinical behaviour.
- Suitability of locoregional or radionuclide approaches.

An important question is when to initiate treatment and whether early aggressive management is indicated or observation in patients who are otherwise asymptomatic is adequate. Traditionally, lack of efficacy of systemic treatments had driven a tendency towards observation, but data are now indicating value in treating low volume disease and that some treatments may prevent long term complications.

Dr Chua noted that in addition to the cytotoxic chemotherapy, SSAs and biologic targeted therapies reviewed in the current presentation, systemic treatment also includes other categories which would not be covered: radionuclide therapy; and the antihistamines, antidiarrheals and other general treatments for symptom management.

**Cytotoxic chemotherapy**

Dr Chua made the following key points made in relation to chemotherapy options.

**Cisplatin + etoposide (small cell lung cancer regimen)**

- Indicated in poorly differentiated/anaplastic/small cell-like tumours; poorly differentiated or small cell lung cancer like tumours seen as the most chemoresponsive of NETs and are very responsive to platinum and etoposide combinations, however, some clinicians now using for high grade (mitotic count >20/10HPF [20 per 10 high power fields] or Ki67>20%) that are not necessarily poorly differentiated.
- Responses between 36–67% reported with median survival of 19 months.
- Fluorodeoxyglucose positron emission tomography (FDG PET) avidity is predictive of response.

**Well differentiated NETs**

- Much more common than poorly differentiated and more difficult from a chemotherapy perspective.
- Generally, only a modest response to chemotherapy although different tumours have different propensity to respond: pancreatic NETs more chemoresponsive than other GI NETs. Thus, it is important to look at proportion of pancreatic tumours in studies as this will influence results.
- Limited contemporary data exist comparing various study treatments to best supportive care; more typically comparisons are between treatments.
- Established agents are streptozotocin + 5FU [5-fluorouracil], dacarbazine and doxorubicin. Emerging agents are temozolomide and capecitabine. Key agents are discussed further below.
- Newer cytotoxic agents with broad spectrum efficacy in other tumour types but with minimal or no efficacy in NET (docetaxel, paclitaxel, gemcitabine, pemetrexed) are not reviewed further.
Streptozotocin +/- 5FU
- Streptozotocin + 5FU is a common regimen for well differentiated NETs.
- Randomised trials showed modest response rates (16–33 %) and wide ranging median survival 11.2–24.3 months.
- Combination appears better than streptozotocin alone in islet cell carcinoma (response 63 versus 36%).
- Dr Chua is unaware of trials comparing this regimen with best supportive care.
- One trial showed that streptozotocin + 5FU produced better survival than doxorubicin/5FU, but excess of small bowel origin tumours in doxorubicin recipients raises questions regarding patient comparability in this trial.
- Streptozotocin is increasingly difficult to get and this may affect availability of this treatment regimen, eg, supply in Australia is low and potentially going out of production.

Dacarbazine
- Modest single agent activity in NET generally (response rates 8.2–16%) but slightly better in pancreatic islet cell carcinoma (response rate 33%).
- Median survival 12–20 months.

Temozolomide (oral form of dacarbazine)
- Looks promising although modest response rates, both alone and in combination with thalidomide.
- Interest in use with capecitabine: retrospective data only and a prospective study may be planned.
- There has been a study to establish whether DNA repair deficiency in the MGMT [O6-methylguanine DNA methyltransferase] enzyme is predictive for response to temozolomide; this appears to be the case as it is with glioblastoma multiforme (GBM). It has also been found that incidence of this MGMT deficiency appears to be higher in pancreatic NETs and lower in non-pancreatic NETs.
- The use of temozolomide in GBM as a radiosensitiser raises the question of whether there is a similar role for temozolomide rather than 5FU for this purpose in NET.

Doxorubicin
- May be of some value: monotherapy response rate 21%, median overall survival 11.1 months.
- Combination with 5FU: response rate 16%, median overall survival 15.7 months.
- Has produced fairly high response rates in combination with streptozotocin in pancreatic NETs: response 6–69%, median survival 20–26 months.

Dr Chua highlighted that symptom management is an important part of managing NET patients and reviewed characteristics of carcinoid syndrome (episodic flushing, wheezing, diarrhea, right-sided heart valve disease) caused by secretion of vasoactive peptides, principally kallikrein.

He noted the tendency to associate carcinoid syndrome with midgut carcinoids, where patients would theoretically have liver metastases before displaying symptoms of carcinoid syndrome. However, in reality, carcinoid syndrome can occur without liver metastases in extra-intestinal NETs.

Somatostatin analogues
Dr Chua noted the following key points regarding SSAs:
- Somatostatin is a native peptide which inhibits endocrine secretion and, thus, inhibits the secretory effects of NET. It is not useful clinically because of its short half-life (<3 min).
- The synthetic peptide analogue of somatostatin octreotide has a half-life of two hours which allows for three-times daily dosing in carcinoid syndrome.
- The current tendency is to use longer acting preparations that allow monthly dosing: Sandostatin® LAR® (octreotide) deep intragluteal injection; Somatuline® Autogel® (lanreotide) deep subcutaneous injection. Efficacy appears to be similar between products but different administration may affect patient preferences.
- Side effects include mild glucose intolerance and gastrointestinal symptoms including nausea, abdominal discomfort, bloating, loose stools, fat malabsorption and ileus. Reduced gall bladder
contractility which can result in asymptomatic gallstones or gallbladder sludge has been reported at levels up to 50% but rates of problematic effects requiring intervention are low (2%). There is debate as to whether there is a role for prophylactic cholecystectomy in these patients.

Indications for SSAs have been in management of carcinoid syndrome symptoms and prevention/management of carcinoid crisis. However, there has been a move towards a lower threshold for starting SSAs even if patients are not clearly symptomatic or symptoms are not especially severe in order to prevent long term complications of disease such as valvular heart disease and mesenteric fibrosis. Dr Chua noted that this may not fit with restrictions on funding for treatment and that these regulations are at odds with international opinion on use of SSAs.

Current consensus on use of perioperative cover with SSAs includes patients with symptomatic or functional tumours or those with bulky disease or high biochemical makers (urine 5HIAA/serum chromogranin A [CgA]). Patients already on SSA therapy should continue with treatment.

Dr Chua noted that in the PROMID study on antiproliferative activity of SSAs, patients with carcinoid syndrome and those with non-functioning tumours benefited similarly and highlighted that presence or absence of tumour functioning should not necessarily therefore influence decisions regarding treatment.

Dr Chua noted that there was an ongoing UK trial using lanreotide vs placebo in non-functioning NETs and a randomised US trial evaluating long-acting pan-receptor agonist pasireotide (SOM230) versus long-acting octreotide in non-functioning tumours.

**Interferon-alpha**

Dr Chua summarised the following regarding interferon-alpha:
- Interferon-alpha tends to be used late in treatment because of toxicity and a cumbersome administration schedule.
- However, it has value in NETs; it may control hypersecretion symptoms and, unlike SSAs, has resulted in some tumour shrinkage although response rates are low.
- It may be of value in combination with SSAs in patients with poorly controlled symptoms on SSA therapy alone but there is no evidence to support up-front combination treatment.

**Treatment response monitoring**

Dr Chua briefly reviewed treatment response monitoring highlighting the value of measuring the two key biochemical markers urine 5HIAA and serum CgA in addition to assessing symptoms and scanning. He noted that there is a logistical problem with these tests, eg, four weeks’ delay to CgA results in Australia, and that planning needs to account for this. He also noted that SSA treatment can reduce serum CgA levels so changes should not always be attributed to other treatment being used.

**Biologic targeted therapies**

The following were key points regarding biologic targeted therapies:
- Bevacizumab (monoclonal antibody against vascular endothelial growth factor [VEGF]):
  - Higher response rate to bevacizumab compared with interferon-alpha and further disease stabilisation when bevacizumab added to effective interferon-alpha treatment.

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3 Carcinoid crisis summarised as follows:
- May be precipitated by tumour manipulation (palpation, biopsy, surgery) or anaesthetic and less commonly occurs after chemotherapy, liver directed therapy or radionuclide therapy.
- Regarded to be more common and a greater risk in patients with extensive tumour bulk and functional tumours.
- Symptoms: hypotension or hypertension, flushing, diarrhoea, tachycardia, arrhythmias, bronchospasm, confusion.
- Intraoperative hypotension can be refractory to standard resuscitation measures.
Bevacizumab in combination with a number of other key chemotherapy agents has resulted in fairly high disease stabilisation rates.

There are trials of other inhibitors of the VEGF pathway, e.g., the tyrosine kinase inhibitor valatinib (PTK787) with VEGF and platelet-derived growth factor (PDGF) receptors as target molecules.

There have been trials of two mTOR inhibitors, temsirolimus and everolimus (RAD001).

mTOR is believed to regulate cancer cell growth by regulating angiogenesis and other functions such as nutrient uptake. Preclinical models have shown mTOR inhibition to be active in NET.

One phase II study with temsirolimus showed a fairly low response rate which the authors described as “little activity” but this was a single arm trial.

Everolimus appears more promising than temsirolimus: use with octreotide resulted in high disease stabilisation rates and reasonable response rates of circa 20%; use in combination with Sandostatin appears to produce an improved disease stabilisation rate.

Activity also been shown with the multikinase inhibitor sunitinib (anti-VEGFR, PDGFR, stem-cell factor receptor, cKIT) and the multi tyrosine kinase inhibitor sorafenib (inhibitor of VEGFR2, FLT3, PDGFR, FGFR1). Interestingly, the toxicity with sorafenib in NET has been more marked than in other cancers where it is used (renal cell carcinoma and hepatocellular carcinoma).

The 26S proteosome inhibitors bortezomib and imatinib have minimal or no activity in NET.

Conclusion

Dr Chua closed by highlighting issues regarding clinical trials design issues in NET, pointing out the following challenges:

- Heterogeneity of the disease (different primary sites, different natural history) and impact on study outcome.
- Difficulty controlling for indications for initiating treatment; patients may have quite different treatment histories and patient selection can greatly influence study outcome.
- Rarity of disease which underlines the need for collaboration in terms of trials groups to get patient numbers needed.
- Difficulty identifying endpoints which will be of value to clinicians. Oncology tends to focus on tumour shrinkage and overall survival which may not necessarily be useful in NET.
- Issue of lack of clarity as to what is standard care for comparison in trials; this affects ability to generalise trial to practice.

Improving the management of GEP NETs: the Australian perspective

Dr Yu Jo Chua, Medical Oncologist, The Canberra Hospital, Canberra, Australia

Dr Chua opened by noting that a key issue exists with the epidemiology of neuroendocrine tumours (NETs) in that the scale of the problem is not known.

Although NETs are described as “rare” tumours, Dr Chua noted:

- Estimated incidence in Australia (2000–2004) of approximately 3.3 per 100,000/year; similar to international incidence figures (2.5–5 per 100,000/year).
- Registry derived figures are likely to underestimate true incidence.
- The indolent nature of disease may possibly mean significantly higher prevalence than appreciated.

CTNZ Neuroendocrine Tumour Workshop, 1 May 2009 – Workshop report
Dr Chua, also noted that, as has been pointed out earlier in the day’s sessions, that US SEER data suggests increasing incidence and higher incidence than that cited above.

The July 2008 Australian Neuroendocrine Tumours (NETs) Consensus Workshop in Melbourne responded to increasing international interest in improving management of NETs, evidenced in:

- Recent publication of international guidelines
  - European NETs Society (ENETS)
  - US National Clinical Cancer Network (NCCN)
  - A National Summit on NETs in September 2007 convened by the US National Cancer Institute.

Dr Chua set out the Melbourne consensus meeting objectives and discussion agenda as set out in table 1.

**Table 1: Australian Neuroendocrine Tumours (NETs) Consensus Workshop, Melbourne July 2008**

<table>
<thead>
<tr>
<th><strong>Meeting objectives:</strong></th>
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<tbody>
<tr>
<td>To understand the consensus and controversies in the management of NETs across international guidelines and to understand the implications for service implementation in Australia.</td>
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<tr>
<td>To develop a minimum diagnostic set and a service model for Australian healthcare professionals involved in the management of NETs.</td>
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<td>To raise the profile of NETs amongst Australian clinicians.</td>
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<tr>
<th><strong>Discussion agenda:</strong></th>
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<tr>
<td><strong>Diagnosis, monitoring and surveillance:</strong></td>
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<tr>
<td>A minimum investigation set, including histopathological testing and serum markers.</td>
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<tr>
<td>Staging (including imaging) and risk stratifying patients.</td>
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<tr>
<td>Monitoring treatment response and surveillance strategies for disease recurrence.</td>
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<tr>
<th><strong>Locoregional treatment:</strong></th>
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<tr>
<td>What are the aims of surgery in GEP-NETs?</td>
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<tr>
<td>The use of liver-directed therapies (chemo-embolisation, SIR-Spheres®, radiofrequency ablation and cryotherapy).</td>
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<tr>
<td>Is there a role for liver transplantation?</td>
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<tr>
<th><strong>Systemic treatment:</strong></th>
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<tr>
<td>Should somatostatin analogues be used in patients with non-functioning or asymptomatic GEP-NETs?</td>
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<tr>
<td>Which patients may benefit from chemotherapy (cytotoxics and targeted agents), and which agents/regimens?</td>
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<tr>
<td>Selecting patients for and improving access to radionuclide treatment</td>
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<tr>
<td>Assessing novel agents.</td>
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<tr>
<th><strong>Service delivery planning:</strong></th>
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<tr>
<td>Should treatment of GEP-NETs occur in specialised centres?</td>
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<tr>
<td>Setting management guidelines and standards.</td>
</tr>
<tr>
<td>Increasing patient access to optimal multidisciplinary care.</td>
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<tr>
<td>Problem areas, hurdles and short falls.</td>
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</table>

Chua presented the following on key recommendations that emerged from the consensus meeting:

- ENETS/NCCN guidelines should be adapted for use within the Australian context. The aim is to inform Australian NETs specialists about available treatment options, but not to be a substitute for specialist care. Dr Chua noted that ENETS recommendations for pathology assessment include: TNM [tumour, node, metastases] classification system and grading system (G1-3: mitotic count, Ki67).
• There needs to be an emphasis on multidisciplinary, individualised, proactive management of NET patients. Proactivity is seen to be key.

• The following initiatives are also supported:
  - database/registry; tissue banking
  - adaptation of guidelines
  - sharing of expertise
  - clinical trials.

Issues in NET management in Australia
The following key factors contributing to issues in NET management in Australia emerged from the discussion.

Limited data on epidemiology and patient outcomes
As set out above there are issues with establishing incidence. Prevalence is a key consideration as longer survival in some patients can mean high numbers and a significant health burden.

The Australian Institute of Health and Welfare (AIHW) collects cancer registry data but only for tumours considered to be “malignant”. It is anticipated that numbers of cases are judged as benign are, therefore, not reported and/or recorded. Limited outcome data are collected and there are no data on management. This creates a situation where there is limited ability to compare results of interventions/improvement initiatives.

Diverse range of specialists involved
There is a diversity of specialists with interest in NETs, including non-oncologists such as gastroenterologists and endocrinologists. Oncologists may have a skewed view of NETs with a bias towards patients with more biologically aggressive disease.

Lack of consensus on management
A lack of consensus about investigations and treatment tends to be compounded by a lack of evidence, in particular from randomised trials.

Limited access to emerging technologies in Australia
A number of factors contribute to limited access to emerging technologies in Australia.

Medicare and Pharmaceutical Benefits Scheme (PBS) regulations can be prohibitive. There is limited randomised clinical trials evidence in NET, particularly for systemic therapies, and thus guideline recommendations need to be based on expert opinion and consensus. However Therapeutic Goods Administration (TGA) approval and the PBS listing, required for reimbursement, is dependent on availability of randomised trials evidence. PBS listings are based on restricted indications and there can be a long lag time before inclusion of a treatment on the schedule.

As a result, drug licensing and reimbursement approval processes are not keeping up with evolving data and expert recommendations. An example is the PBS restriction on somatostatin analogue treatment for patients with non-functioning NETs.

Another example involves bevacizumab in metastatic colorectal cancer. Initial reports of benefit were in 2003 with results of the AVF2107 trial published in the New England Journal of Medicine in 2004. A positive recommendation was made by the Pharmaceutical Benefits Advisory Committee in July 2008 and as at 1 May 2009, parliamentary approval is still awaited.

The combination of state and federal (Medicare) funding for health care in Australia can also affect access to treatment. Funding may then differ between states.
The variances in state and federal (Medicare) medical funding in Australia can create discrepancies in access to certain treatments and can make it difficult to progress treatment improvement initiatives at a national level. For example, off-Medicare treatments have to be funded by local hospital budgets and budgetary constraints may make it difficult for centres with specialised services to treat patients from other states who would not have access to such treatments locally.

Funding issues restrict access to radioisotope imaging and radionuclide therapies. There is no Medicare funding for FDG-PET (fluorodeoxyglucose positron emission tomography) for NETs or for radionuclide therapy, both of which need to be funded through hospital budgets.

Finally, Australia’s diverse geography adds difficulties with regard to access to specialist centres and specialist care.

Other
Other factors raised were an absence of effective models for delivering specialist NET care and difficulties obtaining funding for clinical improvement initiatives versus research. It may be necessary to position clinical improvement work as research to access funding.

Moving forward
The following proposals and initiatives were put forward in the consensus workshop:

- NETs registry and database.
- Virtual multidisciplinary networks built around “capability hubs” with a NETs care coordinator (refer below).
- National guidelines: simplified guidelines developed by working groups drawn from workshop attendees. It is recognised that the definition of best practice presented in the guidelines can also be a valuable tool for driving changes in indications for funding.
- Initiation of clinical trials.
- Patient-driven patient support and lobby group; patient versus clinical/industry perspective is critical.

“Capability hubs” are centres with the core capabilities to deliver a particular aspect of care. They present a patient-orientated solution to management of an uncommon disease where the expertise and facilities required may not currently exist in a single centre. The approach recognises that effective management can be shared across several centres.

It was proposed that working groups could be drawn from the consensus workshop attendees to define criteria for each craft-group based capability hub, such as:

- NETs case load, expertise and experience
- available services and facilities (e.g., functional imaging, interventional radiology, specialised pathology and surgery, radionuclide therapy)
- referral patterns.

A virtual multidisciplinary network would then be able to be created based on a network of capability hubs. This could potentially be state-based and set up to receive referrals from within the state. It would function to provide management advice to referring specialists and to channel onward referrals, where necessary, to the relevant capability hub within the network. The main aim would be to support management of NETs patients by the referring specialist and not to take over or centralise patient care.

Periodic meetings would take place, either face-to-face or by teleconference, to discuss referred cases. Meetings may be hosted by a lead centre within the network.

A NETs care coordinator based each network lead centre would:

- serve as a contact point for referrals to the panel, receiving referrals and providing feedback on network recommendation
- organise the network meetings
• coordinate care of patients who are referred to capability hubs within the network for tertiary care
• collect data for a NETs database and for audit purposes
• act as a specialised resource to all sites and other care coordinators.

**Actions**
The following summarises that actions identified from the consensus workshop:

• Development of NETs special interest group under the auspices of COSA (Clinical Oncological Society of Australia).
• Publication of workshop report.
• Engagement of industry partners and potential funders.
• Establishment of NETs registry and database.
• Establishment of virtual multidisciplinary network pilots.
• Clinical trial(s) work.
• Development of national guidelines.
Panel discussion

The panel discussion was facilitated by Dr Dragan Damianovich and included the following participants:

- Professor Michael Findlay
- Professor Irvin Modlin
- Dr Yu Jo Chua
- Professor Ian Holdoway
- Associate Professor Jonathan Koea
- Dr Kate Moodie
- Dr Michael Rutland
- Professor Richard Stubbs
- Dr Mee Ling Yeong.

Open discussion within the panel and with meeting attendees covered key points in diagnosis and management of gastrointestinal neuroendocrine tumours (NETs) with the aim of identifying standard care of patients with NETs in New Zealand. The discussion also served to initiate consideration of a variety of activities including production of New Zealand guidelines, establishment of national multidisciplinary meetings, development of a database and tumour bank and the promotion of basic and translational research.

Pathology

New Zealand does not have a standardised method for reporting pathological diagnosis of NETs. It is recognised that this would be a useful tool for surgeons and oncologists.

It was proposed that New Zealand utilise the consensus outcome from the recent NET pathology summit held in Miami in February 2009.\textsuperscript{4} The consensus document setting out an agreed minimum dataset and summation classification (grade, state, differentiation) along with recommendations is expected to be available within the third quarter of 2009.

The first requirement for achieving standardised reporting in New Zealand is the establishment of a minimum data set for diagnosis of NETs including assessment of the tumour grade and proliferation index. It was noted that the agreed standard can be promulgated through the Royal Australasian College of Pathologists.

The discussion centred on the appropriate steps for standardising the pathology reporting of NETs:

1. **Confirm diagnosis**
   The use of a panel of stains is important as some tumours will not be identified with all stains. Standard stains are chromogranin A (CgA), synaptophysin, neuron specific enolase and CD56.

2. **Determine hormones secreted**
   The consensus opinion from the Miami summit was that the vast majority of stains used to determine which hormones, peptides, amines, etc are being secreted are not helpful unless required for research purposes. Their use is not routinely recommended.

   However, it was noted that there is a future role for somatostatin receptor (SSR) profiling in treatment selection. For example, the slow-release form of octreotide (Sandostatin\textsuperscript{®} LAR\textsuperscript{®}) may not be effective in certain lesions. More potent somatostatin analogues (SSAs) targeting a wider spectrum of SSRs are currently under development.

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\textsuperscript{4} The summit brought together combining E-NET leaders with US pathologists and clinicians to address debate related to the European and US approaches to pathology reporting for NETs and to work towards consensus.
3. **Evaluate proliferative activity of tumour**

Ki-67 should be used as a marker of proliferative activity in NET. It is also a useful prognostic index, particularly in pancreatic NETs. Ki-67 is not generally needed for the small cell variant.

The minimum requirement is likely to include:
- Immunoperoxidase stain to identify tumour as NET
- Assessing the tumour grade
- Ki-67 count as an indicator of proliferation fraction.

Oncologists should engage pathologists to enhance their understanding of the value of the tests being requested. This should become easier once multidisciplinary teams (referred to below) are established.

**Imaging**

Discussion opened with the following points regarding current use of somatostatin receptor (SSR) imaging in New Zealand:
- Imaging numbers in New Zealand relative to incidence estimates indicate serious underutilisation of radionuclide imaging for NETs (12 cases per year completed versus estimated 80–100 new cases per year in Auckland and 240–320 New Zealand wide [using incidence figures of 6–8/100,000]).
- The accepted international standard is to use an 111-indium octreotide scan early in diagnosis. However, in Auckland, octreotide scans are mainly used for planning of radiolabelled treatment.
- Octreotide scintigraphy is the most expensive test used in New Zealand (NZ$2,200) and cost is borne by the referrer.
- In some centres there has been a tendency to reserve octreotide scintigraphy for diagnostic dilemmas and/or problem decisions and it has not been seen to be critical (or the cost justifiable) in treatment situations where other methods can be used to determine a patient’s positive or negative progress (eg, computed tomography [CT] plus markers).

Octreotide scintigraphy before treatment initiation and for follow-up has become standard in the US after a randomised study in gastrinoma\(^5\) showed that clinical management can be changed in nearly 50% of patients after somatostatin receptor scintigraphy using \(^{111}\)In-labelled octreotide.

Somatostatin receptor scintigraphy is further supported by the recent results from the PROMID study,\(^6\) which suggest better efficacy of SSAs in patients with lower tumour burden.

SSR imaging with radioactive 68-gallium (\(^{68}\)Ga)-octreotate PET/CT is considered to be the most accurate technique currently available for whole-body screening of metastatic neuroendocrine tumour sites and for detecting otherwise occult primary lesions. Data supporting this use are preliminary but the importance of utilising available information was noted.

The following points were raised in relation to setting a minimum standard for use of SSR scintigraphy:
- Peter MacCallum Cancer Institute routinely performs baseline imaging and re-imaging at up to 3-monthly intervals if the focus is on monitoring therapy. However, most patients are only imaged at 12-monthly intervals unless there is clinical or biochemical evidence of disease progression.
- Matching clinical behaviour to frequency of imaging should be standard. It is important to image at 3 months following treatment initiation but there is no need to scan more frequently than 6- or 12-monthly unless clinical markers (CgA) are suggestive of disease progression.

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• A recent study identified CgA as a sensitive marker of relapse or disease progression: CgA was the first marker to indicate tumour recurrence in the majority of radically operated midgut carcinoid patients. To avoid unnecessary and costly examinations in asymptomatic patients, it was suggested that follow-up should comprise twice-yearly measurements of plasma CgA and annual ultrasonography until plasma CgA is elevated or clinical symptoms occur. At that time, all efforts should be made to identify recurrent tumour lesions in order to give the patient the best possible treatment, which, if possible, should be surgical removal of the recurrence. Routine care at the Peter MacCallum Cancer Centre involves 3-monthly estimation of Cg-A levels.

• Some form of cross-sectional imaging of index lesions at 6 to 12-monthly intervals is of value in patients who are being observed, especially when a patient is a candidate for operative or ablative procedures at some point in their disease course.

• In addition to assisting with decisions regarding SSA treatment, SSR scintigraphy also gives information on the changes in the nature of a tumour which demand a change in management strategy.

• New data indicate that all patients with NETs, whether functioning or non-functioning, should benefit from long-acting octreotide. This approach will result in a sharp increase in the use of tests to monitor response and guidelines on imaging intervals will be required.

• Imaging will, to some extent, depend on what is available locally, either octreotide scan or triphasic CT.

• Given the relatively small population in New Zealand, one option for improved cost-effectiveness of procedures and treatment is enhanced identification of patients and resulting higher volumes of diagnosis and treatment.

• At 40 cases per year, it may be cost-effective to purchase a gallium generator and perform \(^{68}\)Ga octreotide positron emission tomography (PET) rather than \(^{111}\)In-octreotide scintigraphy. At 80 cases, it is estimated that the cost could be reduced to one-half of that for octreotide scintigraphy.

### Locoregional treatment

Curative surgical resection, palliative resection, selective internal radiation therapy (SIRT), radiofrequency ablation or cryosurgery options were outlined in general. The following further points were made in regard to locoregional treatment, although the obsolete nature of the term “locoregional” was acknowledged:

• Where primary tumour resection is deemed possible, resection should always be attempted unless the risks outweigh the benefits, particularly in widespread metastatic disease.

• The decision to resect is more difficult in patients with predominantly nodal disease, although surgical resection either of primary tumour or liver disease seems achievable. The best approach in that situation is tumour debulking with continuation of treatment with radiolabelled agents (eg, lutetium-octreotide therapy).

• In patients with metastatic disease, there is a tendency not to operate on primary tumours particularly where they are not causing symptoms. There is a need for prescriptive guidelines related to the use of surgery in patients with metastatic disease that emphasise the benefits of primary tumour resection in slow growing tumours. In more aggressive variants (small cell end of the spectrum) with a short natural history, resection of the primary tumour is not recommended since metastatic disease is a predominant cause of morbidity and usually requires systemic treatment.

• It is very difficult to be definitive regarding liver directed treatment and it is essential to assess each patient individually. However, it is generally known that in non-functioning and more markedly functioning tumours, debulking of liver disease may result in better control of symptoms. There is also evidence of prolonged survival with such an approach, although mainly from single institution retrospective series.\(^7\)\(^8\)\(^9\)

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There is a role for judicious use of various ablation therapies (eg, RFA, [chemo] embolisation or SIRT, alone or in conjunction with surgery possibly early in the course of the disease. SIRT in particular may be an early option for more aggressive tumours (eg \( \text{Ki-67} > 20\% \)) with predominant hepatic disease but further evidence is needed.

Further discussion regarding SIRT raised the following points:
- Experience with SIRT (although not largely in NETs) has indicated that patients with a smaller volume of liver disease are at higher risk of ablation of normal liver tissue compared with patients with a higher volume of liver disease. Liver injury may not be a problem with single treatment but cumulative toxicity is a problem with repetitive treatments, particularly if liver resection is still an option.
- Based on the above, there is a tendency to select patients for SIRT who have moderate amount of liver disease or who have particularly symptomatic liver disease.
- Where a tumour is not initially resectable, SIRT can be used upfront to reduce the amount of disease which may make resection possible. If SIRT achieves a significant response, surgery may be preserved for relapse or progression of the disease.
- In spite of promising initial results, the use of SIRT has been limited because of the lack of prospective, randomised studies. It was noted that the opportunity exists for more clinical research, particularly if current phase III trials in metastatic colorectal cancer are successful. However, trials in NETs would need to be multicentre, international initiatives because of the relatively low incidence of NETs.

Liver transplantation
Liver transplantation has had a limited role in the management of NETs. Interest in transplantation has increased with the living donor programme although there is insufficient evidence to support this strategy as primary or salvage therapy. It was noted that the vast majority of NET patients would be declined automatically on MILAN criteria because of extrahepatic disease.

It was also noted that there have been examples where NET patients with severe liver disease developed more aggressive disease post-liver transplant once on immunosuppressive therapy.  

Systemic treatment
Role of interferon (interferon-alpha)
Interferon is effectively first line treatment in New Zealand in non-functioning disease since current funding excludes treatment with SSAs. However, interferon is associated with severe flu-like side effects which, while they may ameliorate in six weeks, usually persist in the majority of patients. It also may induce fibrosis. On that basis, it is difficult to use long term.

Interferon use is more popular in northern Europe (Öberg) than the rest of the world. The US practice is to add interferon only if SSA in maximum dose is ineffective in controlling symptoms or with the escape phenomenon with SSA. If quality of life is paramount in the treatment of NETs, use of interferon will be difficult to sustain.

Somatostatin analogues (Sandostatin)
On the basis of the results of the PROMID study, the general opinion is that all NET patients, with either functioning or non-functioning tumours, should have access to long-acting octreotide. This will have significant implications on funding in New Zealand where SSAs are currently only funded for the control of carcinoid syndrome.

However, it was agreed that the extension of funding should be sought to include patients with non-functioning NETs.

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The following points were made in relation to this:

- There will be a stronger case once the PROMID study is published.
- A local cost-benefit analysis will be required.
- The risk exists that authorities will restrict use to the low volume disease group which derived a larger benefit in the study.
- Clear guidelines on SSA use may help the application for extension of funding.
- While the application is being processed, a self-funding option could be offered to patients with non-secretory tumours.
- Establishment of a patient advocacy group may assist.

Ways to predict response were also discussed:

- 80% of patients with a positive octreotide scan will benefit from SSA treatment.
- Current octreotide scans use analogues targeting somatostatin receptors 2 and 5. Patients with low octreotide uptake might have tumours expressing other receptors and could benefit in the future from newer and more potent SSAs targeting receptors 1, 3 or 4.
- Krenning scale 4 and 5 predict response but this does not preclude the possibility of response from those with other Krenning scale values.

Radiolabelled treatment

The feasibility of developing a New Zealand centre for delivery of the most effective radiolabelled treatments (eg, radioactive lutetium) was discussed. Establishing lutetium treatment for New Zealand requires re-acquisition of ancillary expertise that has been lost (eg, radiopharmacists and physicists) and funding (circa $150,000 for machine plus costs for labelling material). It is possible but would certainly involve much work and may require consideration of options like autoradiopharmacies. It may be more cost-effective to use Australian facilities, if feasible, but this precludes the ability to generate the required expertise for a local facility in the future.

Similar issues exist internationally. US and European regulatory authorities have not agreed to lutetium treatment because of a lack of prospective randomised trials.

It was also noted that New Zealand is not likely to have enough demand for lutetium treatment to be commercially viable. The population of 25 million in Australia and New Zealand is likely to justify the establishment of only one or two centres in total.

Pathways and guidelines in diagnosis and management

Guidelines

The development of guidelines for the diagnosis and management of NETs is imperative and urgent. Discussion highlighted the merits in development of mutual Australasian guidelines with specifics of application tailored to each country based on treatment availability. It was noted that this option depends on Australian agreement to cooperate.

It was emphasised that New Zealand has an opportunity to “leap frog” in management of NETs using effective options developed and advanced overseas.

There was considerable debate regarding the merit of guidelines that promote procedures that cannot be implemented without major resource implications (eg, in terms of procedure availability, geographic access, funding issues, etc). However, there was general agreement that guidelines:

- Need to balance goals versus practical considerations but lack of access to treatment should not dictate the practice promoted.
- Must acknowledge best practice internationally and, as such, will provide a tool for instituting change in New Zealand.
- Should not be static; they should change and evolve to meet changing circumstances and resources.
- Should comprise both best practice and a minimum standard of care.
- Should incorporate the mechanisms for timely implementation of new treatments.
Organisation of care
The unmet requirement for establishment of multidisciplinary teams (MDTs) was highlighted and it was suggested that a first step in addressing this may be to form a panel of experts from different specialties at a national level who would meet (possibly via videoconference) on a monthly basis to discuss cases. The referral process and responsibilities of such a panel will need to be considered. One duty of such a panel may be monitoring of the implementation of guidelines and their impact on treatment decisions. The panel would also provide a forum for increasing awareness, educating relevant parties in NET management and establishing standards of care at different levels.

Such an approach would support a key factor in effective treatment: the requirement for individualised care.

The following points were made in relation to organisation of care for NETs in New Zealand:
- There is recognised value in the six cancer centres in New Zealand providing a potential vehicle for the MDT model of care. Currently centres may not have an endocrinologist or specialist liver surgeon but could be a potential vehicle for developing a team for NET management.
- Centres of excellence are a good fit with the Ministry of Health emphasis on equitable access to care.
- The merit in a national centre for sharing of expertise and applying standard national management is acknowledged but it was also noted that local MDTs are needed for follow-up and maintenance treatment.
- The chosen structure needs to account for future shifts towards virtual centres of excellence and remote care delivered via technology options including interactive television, WebEx, etc (highlighted Sony investment in US for this approach to home based care delivered from physicians sited in hospital).
- A variety of experts is required in NET management and it was noted that “active” hepatic surgeons are the scarcest commodity.
- The National Medical Oncology group with sub speciality groups is of value but these groups need to include endocrinologists and surgeons.
- One difficulty is that existing MDTs tend to be based on regional anatomy (eg, upper GI MDT involves an oncologist, gastroenterologist and surgeon but not an endocrinologist). It will be a conceptual jump in New Zealand to use a disease categorisation approach to MDT.
- The future structure will need to acknowledge and work alongside existing MDTs. One option is to funnel patients to the NET MDT. Typically, only patients needing expertise and advice on highly specialised interventions (eg, liver surgery, suitability for radiolabeled treatment, SIRT) would usually be discussed.
- There is a need for guidelines to underpin the work of the regional MDTs and criteria for the referral of difficult cases to the national virtual NET MDT.

In summary, there was general agreement that in New Zealand with its small size, one virtual centre of excellence is likely to be adequate but with the possibility of distribution of care to the regional centres which have expertise in various specialised procedures.

Research
Establishment of tumour banks and clinical databases is a goal in the management of a variety of cancers and the group endorsed development of these for NETs. It was noted that it may be possible to develop these through clinical trials and that it is typically easier to fund data bank activity as an adjunct to a trial than it is to achieve standalone funding.

Cancer Trials New Zealand (CTNZ) is in a position to set up a database or a NET registry, utilising existing software. However, there is a need to consider hosting by other groups, such as the Australasian Gastrointestinal Trials Group, which could have the advantage of a larger joint population. Alternatively, operating tumour banks with structures independent of research groups may strengthen their governance.

Tumour banks and clinical databases are seen to be critical as the future of further developments in diagnosis and management of NETs is expected to be through better understanding of molecular biology and pathology. There is value in storing histopathological samples, blood samples, etc. It was highlighted...
that New Zealand would benefit from younger doctors gaining international experience and bringing that expertise back to New Zealand. Time spent in leading institutions for NET research would highlight opportunities for such research in New Zealand.

**Action plan**
Several initiatives emerged from the panel discussion:

1. **Development of guidelines for the management of NETs (Dragan Damianovich and Yu Jo Chua)**

   It was considered desirable that Australia and New Zealand develop a joint approach to development of guidelines. Dr Yu Jo Chua will take the proposal to the Australian NETs special interest group, developed under the auspices of COSA, who are to meet in the third quarter of 2009.

2. **Standardisation of reporting of histology results (Mee Ling Yeong)**

   Professor Irvin Modlin promised assistance in obtaining the document from the NET pathology summit held in Miami in February 2009, which should provide standardised classification of NET.

3. **Submission of application for the extension of funding for long acting octreotide (Sandostatin® LAR®) to non-functioning NETs (Dragan Damianovich)**

   It was suggested that the best way to approach the submission would be through the New Zealand Association of Cancer Specialists (NZACS) Gastrointestinal Specialist Interest Group.

4. **Establishment of a National Multidisciplinary Team and virtual Centre of Excellence for the management of NETs**

   A monthly teleconference was proposed as a suitable start point. Discussion would be limited to more complex cases.

5. **Establishment of the national database for NETs (Professor Michael Findlay)**

   It was proposed that the national database be established through CTNZ.
Acknowledgements

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CTNZ would like to acknowledge and express appreciation to the workshop convenors Dr Dragan Damianovich and Dr Amanda Ashley.

Thanks are also extended to Dr Dragan Damianovich for facilitating the panel discussion and to the members of that panel:
- Professor Michael Findlay
- Professor Irvin Modlin
- Dr Yu Jo Chua
- Professor Ian Holdoway
- Associate Professor Jonathan Koea
- Dr Kate Moodie
- Dr Michael Rutland
- Professor Richard Stubbs
- Dr Mee Ling Yeong.

Finally, CTNZ expresses thanks to the workshop presenters:
- Professor Irvin Modlin, Surgical Oncologist, Yale University School of Medicine, New Haven, Connecticut, US
- Dr Yu Jo Chua, Medical Oncologist, The Canberra Hospital, Canberra, Australia
- Dr Dragan Damianovich, Medical Oncologist, Auckland
- Dr Kate Moodie, Radiologist and Nuclear Medicine Specialist, The Peter MacCallum Cancer Institute, Melbourne, Victoria, Australia
- Professor Richard S Stubbs, Gastrointestinal Surgeon, Wakefield Hospital, Wellington
- Dr Mee Ling Yeong, Pathologist, Diagnostic Medlab, Auckland
Appendix 1: Workshop programme

Cancer Trials New Zealand
Invites You To
Neuroendocrine Tumour Workshop 2009
Auckland Hospital, Auditorium. 2 Park Road, Grafton, Auckland
Friday 1 May 2009

I will / will not be attending the Neuroendocrine Tumour Workshop on Friday 1 May (please circle)

Title: __________________________  First name: __________________________  Last name: __________________________
Email: __________________________  Phone: __________________________

PROGRAM OVERVIEW

8.30 – 8.35  Introduction
Professor Michael P Findlay
Medical Oncologist, Director, Cancer Trials
New Zealand, Auckland

3.35 – 8.50  Scope of the problem in New Zealand
Dr Dragan Damjanovitch
Medical Oncologist, Auckland

Chair: A/Professor Jonathan Koza

8.50 – 9.20  Pathology of NETs
Dr Mee Ling Yeong
Pathologist, DML, Auckland

9.20 – 9.50  Loco-regional treatment of NETs
Professor Irvin M Modlin
Surgical Oncologist, Yale University School of Medicine, New Haven, Connecticut, USA

9.50 – 10.10  Questions

10.10 – 10.30  Break
Chair: Dr Michael Rutland and Dr Amanda Ashley

10.30 – 11.00  Radiolabelled modalities in imaging and treatment of NETs
Dr Kate Moodie
Centre for Molecular Imaging,
The Peter MacCallum Cancer Centre

11.00 – 11.15  Role of SIRT in the treatment of NET
Professor Richard S Stubbs
Gastrointestinal Surgeon, Waikfield Hospital, Wellington

11.15 – 11.45  Updates on Medical Oncology options
Dr Yu Jo Chua
Medical Oncologist, Canberra, Australia

11.45 – 12.00  Questions

12.00 – 13.00  Lunch
Chair: Dr Dragan Damjanovitch

13.00 – 13.20  Australian perspective on management of GEP NET
Dr Yu Jo Chua
Medical Oncologist, Canberra, Australia

13.20 – 15.30  PANEL DISCUSSION
Participants:
Professor Irvin M Modlin
Professor Michael P Findlay
Dr Mee Ling Yeong
Dr Yu Jo Chua
A/Professor Jonathan Koza
Professor Richard S Stubbs
Dr Michael Rutland

Please RSVP by Fax: +64 9 373 7927 or email: k.naicker@auckland.ac.nz by 17 April
If you require flights and are NOT attending the prior evening meeting on Thursday 30 April with Professor Irvin Modlin
please contact Kasturi Naicker
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