APNETS
Asia Pacific NeuroEndocrine Tumour Society

# 4TH CONFERENCE OF THE Asia Pacific Neuroendocrine Tumour Society (APNETS)

**13th - 15th October 2016**
**G Hotel Penang**
**Malaysia**

**www.apnets.org**

**Souvenir Programme & Abstract Book**

THE NET ALLIANCE INTEREST GROUP

# Recommended Parameters for Gastroentero-Pancreatic Neuroendocrine Tumours (GEP-NETs) Pathology Report

## WHO Classification of Neuroendocrine Neoplasm of the Gastroentero-Pancreatic system (GEP-NETs)

| WHO 1980 | WHO 2000 | WHO 2010 |
|---|---|---|
| I. Carcinoid | 1. Well-differentiated endocrine tumour (WDET)<br>2. Well-differentiated endocrine carcinoma (WDEC)*<br>3. Poorly differentiated endocrine carcinoma/ small-cell carcinoma (PDEC) | 1. Neuroendocrine tumor Grade 1 (carcinoid)<br>2. Neuroendocrine tumor Grade 2*<br>3. Neuroendocrine carcinoma Grade 3 large-cell or small-cell type |
| II. Mucocarcinoid<br>III. Mixed forms carcinoid-adenocarcinoma | 4. Mixed exocrine-endocrine carcinoma (MEEC) | 4. Mixed adenoneuroendocrine carcinoma (MANEC) |
| IV. Pseudotumour lesions | 5. Tumour-like lesions (TLL) | 5. Hyperplastic and preneoplastic lesions |

* If the Ki67 index exceeds 20%, the NET may be labeled G3

Bosman FT, et al. *WHO Classification of Tumours of the Digestive System.* Lyon, France: IARC Press; 2010.

An adequate pathology report for GEP-NET must have the following minimum parameters:

Organ : ---------- Procedure : ----------

- Size : ---------- cm
- Lymphatic / venous / perineural invasion
- Extent of invasion: ----------
- Resection margin: ----------
- IHC : Chromogranin A (positive/negative) and Synaptophysin (positive/negative)
- Mitoses (<2 / 2-20 / >20)/10 HPF
- % Ki67 (≤2 / 3-20 / >20) State the percentage: ____%
- Diagnosis:
  - ☐ Neuroendocrine tumor, well differentiated, Grade 1
  - ☐ Neuroendocrine tumor, well differentiated, Grade 2
  - ☐ Neuroendocrine carcinoma, poorly differentiated, Grade 3 (Small cell / Large cell NEC)

*Malaysian J Pathol 2013; 35(1) : 107 – 108*

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# WELCOME MESSAGE

On behalf of the Asia Pacific Neuroendocrine Tumour Society [APNETS], I welcome you to the 4th Conference of the Asia Pacific Neuroendocrine Tumour Society [APNETS] being held in Penang, Malaysia from 13th to 15th October 2016. This conference aims to bring together experts in the field of neuroendocrine tumour disease to discuss the latest developments and best practices in its management.

The primary objective of the Asia Pacific Neuroendocrine Tumour Society [APNETS] is to improve the understanding and management of neuroendocrine tumour (NET) disease in the Asia Pacific region.

The APNETS Conference 2016 is planned for healthcare professionals, researchers and scientists from a whole array of different specialties of surgery, internal medicine, oncology, endocrinology, pathology, gastroenterology, diagnostic and interventional radiology and nuclear medicine. Leading experts from around the world will deliberate on the various aspects of diagnosis and management of NET. This year's conference will also have a consensus development workshop on the diagnosis and management of gastrointestinal and pancreatic neuroendocrine tumours.

As in our previous conferences, this conference will certainly provide you an opportunity to update your professional knowledge with the latest in the science of neuroendocrine tumour disease and also to network with experts and fellow colleagues in this field.

The venue of this year's conference is also the G Hotel, located on the scenic seafront promenade, the Gurney Drive in Georgetown, Penang. Gurney Drive is not only famous for its hawker food but also for the many shopping arcades, hotels and luxury condominiums. We hope that you will also be able to unwind and enjoy the alluring charms, sights and sounds of Penang.

I welcome you all to Penang, the 'Pearl of the Orient'.

**Harjit Singh, MBBS, FRCSE, FRCSI**
Organising Chairman, APNETS Conference 2016 &
President, Asia Pacific Neuroendocrine Tumour Society

# APNETS COUNCIL/ORGANISING COMMITTEE

## APNETS Council 2015-2016

| | |
|---|---|
| **President** | Datuk Dr. Harjit Singh<br>*Consultant Surgeon, Prince Court Medical Centre, Kuala Lumpur, Malaysia* |
| **Vice-President** | Professor Dr. Yau Chung Cheung, Thomas<br>*Consultant Medical Oncologist, Department of Medicine, University of Hong Kong, Hong Kong, China* |
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| | Professor Dr. Chin-Yuan Tzen<br>*Consultant Pathologist, Cathay General Hospital, Taipei, Taiwan* |
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| **Auditors** | Dr. R. Krishnan<br>*Consultant Surgeon, Hospital Selayang, Selangor, Malaysia* |
| | Dr. Shahrina Man Harun<br>*Consultant Interventional Radiologist, Pantai Hospital, Bangsar, Kuala Lumpur, Malaysia* |

## Organising Committee

| | |
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| **Organising Chairman** | Datuk Dr. Harjit Singh<br>*Prince Court Medical Centre, Kuala Lumpur, Malaysia* |
| **Scientific Chairman** | Associate Professor Dato' Dr. Fuad Bin Ismail<br>*Universiti Kebangsaan Malaysia, Kuala Lumpur, Malaysia* |
| **Programme Committee** | Professor Datuk Dr. Looi Lai Meng<br>*University of Malaya, Kuala Lumpur, Malaysia* |
| | Dr. R. Krishnan<br>*Hospital Selayang, Selangor, Malaysia* |
| | Datin Dr. Sharmila Sachithanandan<br>*Sime Darby Medical Centre, Subang Jaya, Selangor, Malaysia* |
| | Dr. Zanariah Hussein<br>*Hospital Putrajaya, Putrajaya, Malaysia* |
| | Dr. Tan Teik Hin<br>*National Cancer Institute, Putrajaya, Malaysia* |

# PROGRAMME OVERVIEW

## Thursday, 13th October 2016

| | |
|---|---|
| 13:30 – 17:00 | Registration |
| 14:00 – 18:45 | Consensus Development Workshop on the Diagnosis and Management of GEP-NETs |
| 20:00 – 22:00 | Welcome Dinner |

## Friday, 14th October 2016

| | |
|---|---|
| 07:30 – 17:00 | Registration |
| 08:25 – 08:30 | Welcome Remarks |
| 08:30 – 10:30 | Scientific Session I |
| 10:30 – 11:00 | Tea / Coffee Break |
| 11:00 – 12:30 | Scientific Session II |
| 12:30 – 14:00 | Lunch Symposium [Ipsen] |
| 14:20 – 16:30 | Scientific Session III |
| 16:30 – 16:45 | Tea / Coffee Break |
| 16:45 – 17:45 | Tea Symposium [Novartis] |
| 17:45 – 18:45 | APNETS Council Meeting |

## Saturday, 15th October 2016

| | |
|---|---|
| 08:30 – 10:30 | Scientific Session IV |
| 10:30 – 11:00 | Tea / Coffee Break |
| 11:00 – 12:35 | Scientific Session V |
| 12:30 – 12:35 | Closing Remarks |
| 12:35 – 13:30 | Lunch |

# SCIENTIFIC PROGRAMME

| TIME | TOPIC | SPEAKER |
|---|---|---|
| **Thursday, 13th October 2016 - Salon 3** | | |
| **CONSENSUS DEVELOPMENT WORKSHOP** | | |
| **Consensus Development on Diagnosis of GEP-NETs** | | |
| 14:00 | Introduction | |
| 14:15 | Pathology : Minimum Standards in Cytopathological reporting of GEP-NETs | Nirush Lertprasertsuke [Thailand] |
| 14:30 | Biomarkers : Role of Biomarkers in the Diagnosis & Management of GEP-NETs | Amir Sharifuddin Mohd Khir [Malaysia] |
| 14:45 | Imaging : Role of Imaging in Diagnosis of GEP-NETs | Basri Johan Jeet Abdullah [Malaysia] |
| 15:00 | Discussion | |
| **16:00** | **Tea / Coffee Break** | |
| **Consensus Development on Management of GEP-NETs** | | |
| 16:15 | Surgery : Role of Surgery in Management of Primary GEP-NETs | Vivek A. Saraf [India] |
| 16:30 | Surgery : Role of Surgery in Management of Metastatic GEP-NETs | Liau Kui Hin [Singapore] |
| 16:45 | Radionuclide : Role of Radioisotopes in Diagnosis and Treatment of GEP-NETs | Tan Teik Hin [Malaysia] |
| 17:00 | Medical : Medical [Somatostatin Analogues] Management of GEP-NETs | Zanariah Hussein [Malaysia] |
| 17:15 | Oncology : Cytotoxic & Targeted Therapies for GEP-NETs | Thomas Yau Chung Cheung [Hong Kong] |
| 17:30 | International Radiology : Role of Interventional Radiology in the Treatment of GEP-NETs | Mohd Rizal Roslan [Malaysia] |
| 17:45 | Discussion | |
| **20:00** | **Welcome Dinner** | |

# SCIENTIFIC PROGRAMME

| Friday, 14th October 2016 - Ballroom 2 | | |
|---|---|---|
| **08:25** | **Welcome Remarks** | Fuad Ismail [Malaysia] |
| | **Session I: Gastrointestinal NETs – Diagnosis and Investigation**<br>**Chairpersons: Zanariah Hussein / Thomas Yau Chung Cheung** | |
| 08:30 | Hallmarks on Neuroendocrine Tumour Development | Kjell Öberg [Sweden] |
| 09:00 | Symptoms and Investigations | Sharmila Sachithanandan [Malaysia] |
| 09:20 | Radiological Imaging | Basri Johan Jeet Abdullah [Malaysia] |
| 09:40 | Pathological Classification | Looi Lai Meng [Malaysia] |
| 10:00 | Case Discussion [Pitfalls of CGA Testing] | Harjit Singh [Malaysia] |
| 10:10 | Serum Biomarkers in the Management of NETs | **Panel Discussion**<br>Kjell Öberg [Sweden]<br>Frank Ulrich Pape [Germany]<br>Rodney J. Hicks [Australia]<br>Amir Khir [Malaysia]<br>Looi Lai Meng [Malaysia] |
| **10:30** | **Tea / Coffee Break** | |
| | **Session II Pancreatic NETs**<br>**Chairpersons: Tan Teik Hin / Vivek A. Saraf** | |
| 11:00 | Molecular Imaging : FDG PET, DOTATATE or Both | Rodney J. Hicks [Australia] |
| 11:20 | Somatostatin Analogues / Anti-Tumour Effect | Marianne Pavel [Germany] |
| 11:40 | Case Discussion [Functional NETs] | David Tai Wai-Meng [Singapore] |
| 12:00 | Management of Non-Secretory Diarrhoea | Frank Ulrich Pape [Germany] |
| **12:30** | **Lunch Symposium [IPSEN]**<br>**Dual Perspectives in GEP-Net Management – Patients and Doctors** | |
| | **Session III: Management of GEP/NETs**<br>**Chairpersons: Looi Lai Meng / Manisekar Subramaniam** | |
| 14:20 | Should Ki67 Decide the Chemotherapy Regimen in G3 NEC? | David Tai Wai-Meng [Singapore] |
| 14:40 | Debate:<br>Medical Treatment, NOT PRRT should be the 1st Line Therapy for Non-Resectable Neuroendocrine Tumours. | |
| | • Medical Therapy | Marianne Pavel [Germany] |
| | • PRRT | Rodney J. Hicks [Australia] |
| 15:20 | Surgical Management of GEP NETs - The Tata Memorial Hospital Experience | Shailesh V. Shrikhande [India] |
| 15:40 | Theranostics in NETs - From Imaging to Radioguided Surgery and Therapy | Sugandha Dureja [India] |
| 16:00 | Immunotherapy, Is It a Valid Alternative for NETs? | Kjell Öberg [Sweden] |
| **16:30** | **Tea / Coffee Break** | |
| **16:45** | **Tea Symposium [Novartis]**<br>**Update on the GEPNET Consensus Guidelines and the Future of NET** | |
| **FREE EVENING** | | |

# SCIENTIFIC PROGRAMME

| Saturday, 15th October 2016 - Ballroom 2 | | |
|---|---|---|
| | **Session IV: Lung NETs**<br>**Chairpersons: Premnath N. / Rodney Hicks** | |
| 08:30 | Classification and Diagnosis | Nirush Lertprasertsuke [Thailand] |
| 08:50 | Carcinoid and Other Paraneoplastic Syndromes – An Update on Management | Norasyikin A. Wahab [Malaysia] |
| 09:10 | Management of Lung NETs | |
| | • Surgery | Anand Sachithanandan [Malaysia] |
| | • Radiotherapy | Fuad Ismail [Malaysia] |
| | • Medical Therapy | Thomas Yau Chung Cheung [Hong Kong] |
| 10:00 | Case Disscussion [Lung NET & Media Stinal NET] | Fuad Ismail [Malaysia]<br>Zanariah Hussein [Malaysia] |
| **10:30** | **Tea / Coffee Break** | |
| | **Session V: Consensus Workshop**<br>**Chairpersons: Sharmila Sachithanandan / Liau Kui Hin** | |
| 11:00 | NET G3 - Fact or Fiction? | Frank Ulrich Pape [Germany] |
| 11:20 | Presentation of Workshop Outcomes:<br>Asia Pacific Consensus on Diagnosis & Management of GEP- NETs | Krishnan [Malaysia]<br>Fuad Ismail [Malaysia] |
| 11:50 | Discussion on Consensus | |
| 12:30 | Closing Remarks | Harjit Singh [Malaysia] |
| **12:35** | **Lunch** | |

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# CONFERENCE INFORMATION

**Conference Venue**
The 2016 APNETS Conference is held at the G Hotel, located along the scenic Gurney Drive in Penang, starting on Thursday, 13th October 2016 and finishing on Saturday, 15th October 2016.

**Registration Desk**
The Registration Desk is located on Level 2 of the G Hotel and is open as follows:
13th October 2016 [Thursday]
from 13:00 to 17:00
14th October 2015 [Friday]
from 07:00 to 17:00

Please collect your conference bag and attendance certificate from the registration desk prior to entering any of the conference sessions.

**Identification Badges**
Identification [Name] badge is essential for entry to all conference sessions and to take part in all conference activities.

**Registration Entitlements**
Delegates will be entitled to:
- Welcome Reception
- Admission to Scientific Sessions and Exhibition
- Conference Bag and Materials
- Conference Attendance Certificate
- Coffee / Tea / Lunch

**Welcome Reception**
13th October 2016 [Thursday]
The Welcome Reception will be held at the Grand Ballroom, Level 2, G Hotel
Dress Code: Smart Casual

**Speakers Support**
All speakers are requested to report to the Speaker Preparation Room at least two hours prior to their presentation or the day before [for the presenters in the morning sessions]. There will be technicians to assist with loading your slides for presentation.

The Speaker's Preparation Room is located at Salon 2, Level 2, G Hotel and the operating times are:
13th October 2016 [Thursday]
from 10:00 to 17:00
14th October 2016 [Friday]
from 07:00 to 17:00
15th October 2016 [Saturday]
from 07:00 to 12:00

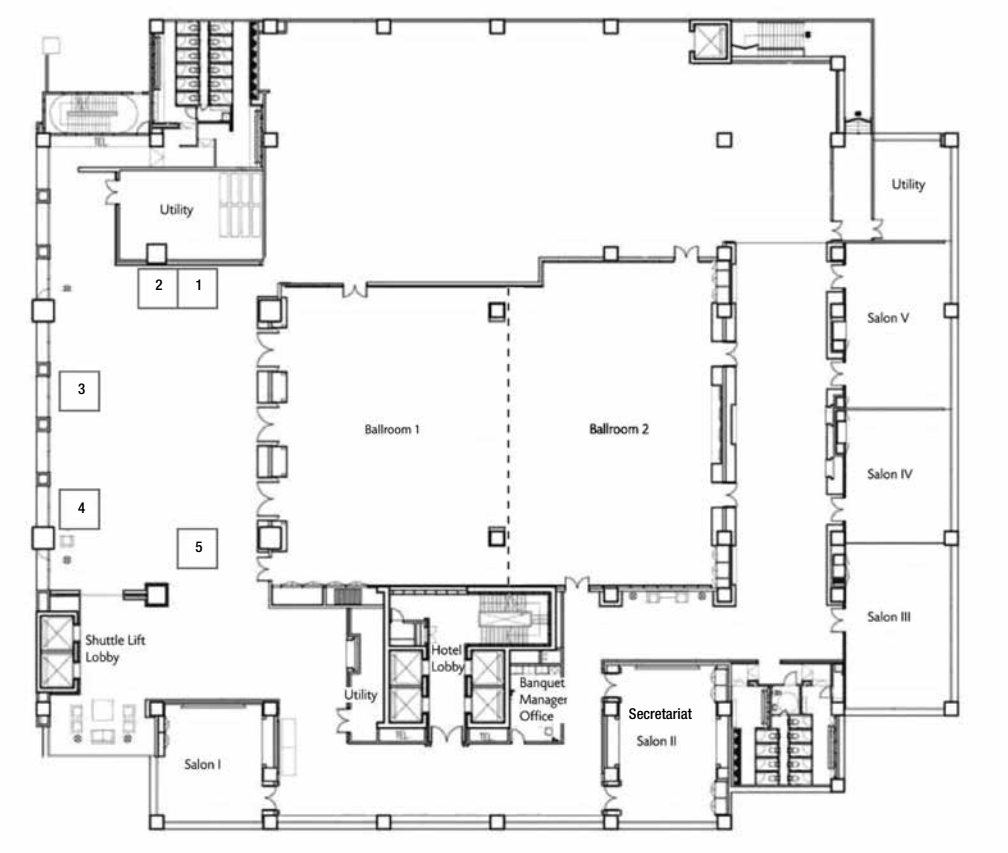
**Photography and Video Recording Policy**
Non-designated personnel are not allowed to photograph or video record any presentations during the scientific sessions.

**Mobile Phones**
For the convenience of all delegates, please ensure that your mobile phone is put on "silent" mode during the conference sessions.

**Liability**
The Organising Committee shall not be liable for any personal accidents, loss or damage to private properties of participants during the conference.
Participants should make their own arrangements with regard to their personal travel insurance.

**DISCLAIMER** Whilst every attempt would be made to ensure that all aspects of the Conference as mentioned in this publication will take place as scheduled, the Organising Committee reserves the right to make last minute changes should the need arises.

# TRADE EXHIBITION




| Booth | Company |
|---|---|
| 1. | IPSEN |
| 2. | Diagnostic System Sdn Bhd |
| 3. | Cisbio Bioassays |
| 4. | Thermo Fisher Scientific |
| 5. | Novartis Malaysia Sdn Bhd |

**DR DAVID TAI WAI-MENG**
Consultant Clinical Oncologist
Division of Medical Oncology
National Cancer Centre Singapore
Singapore

PRESENTATION

## Case Discussion

Few and far between functional NETs
There will be a case discussion on two rare functional NETs.

## Should Ki67 Decide the Chemotherapy Regimen in G3 NEC?

The understanding of high grade NET/NEC is evolving. While Ki67 of 55% has been mooted to be an optimal cut-off in prognostication and predictive marker for response with platinum based chemotherapy, other factors needs to be considered.

**PROFESSOR RODNEY J. HICKS**
The Peter MacCallum Cancer Centre,
Melbourne, Australia

PRESENTATION

# Debate: Medical Treatment, NOT PRRT should be the 1st Line Therapy for Non-Resectable Neuroendocrine Tumours. The Case Against

Many therapeutic options confront clinicians faced with selecting the optimal therapy for patients with advanced NET. Current guidelines reserve peptide receptor radionuclide therapy (PRRT) for patients who have failed other medical therapies. For low-grade NET somatostatin analogue (SSA) is recommended for symptomatic and now asymptomatic NET based on the anti-proliferative effects suggested by the PROMID and CLARINET trials. For patients who fail this treatment, randomized clinical trial data support the use of the mTOR inhibitor, everolimus, and the multi-targeted tyrosine kinase inhibitor, sunitinib. Despite the high level of evidence in support of these approaches, the evidence for efficacy is underwhelming, with low objective response rates and rather unimpressive prolongation of progression-free survival and no evidence of overall survival advantage if treatment is delayed until progression is confirmed. Moreover, these therapies have substantial side-effect profiles that may diminish quality of life rather than improving it, which should be a treatment objective for any non-curative treatment. Results of chemotherapy in even higher-grade NEC are similarly disappointing with low response rate, short duration of benefit and substantial toxicity. The experience of many individual centres delivering PRRT is that it provides a relatively high and durable disease control rate with low toxicity. These institutional reports have been supported by the preliminary reports of the NETTER-1 randomised control trial of Lu-177 DOTATATE PRRT versus dose escalation of SSA therapy. Quality of life measures are awaited but institutional series suggest that this is generally improved with PRRT irrespective of response. Head-to-head trials comparing other medical therapies with PRRT are planned or in progress. Compassion demands that the most effective and least toxic therapy should always be used first in treating cancer. Current evidence suggests that this is PRRT in cases that are suitable for this therapy.

**PROFESSOR RODNEY J. HICKS**
The Peter MacCallum Cancer Centre
Melbourne, Australia

PRESENTATION

# Molecular Imaging of Neuroendocrine Tumours: FDG PET, DOTATATE or both

Neuroendocrine tumour (NET) is generally an indolent disease with a long natural history and rather non-specific symptoms. Due to these factors, it often presents as advanced metastatic disease. Many patients are, accordingly, unsuitable for surgery at diagnosis and require systemic treatment. The choice of this treatment is highly dependent on tumour biology, which, in turn, is significantly influenced by tumour grade. Although biopsy is considered to be the gold standard for grading, tumour heterogeneity can lead to unrepresentative sampling. Low-grade tumours, which constitute the majority of NET, retain many of the characteristics of the cells from which they arise, including expression of the somatostatin receptor (SSTR) and the ability to secrete various biological compounds including neuropeptides and bioamines. The SSTR is thus both a diagnostic and therapeutic target. This has been leveraged through the use of somatostatin analogue (SSA) imaging and therapy. In recent years the availability of 68Ga generators has enabled SSA imaging of various ligands that have high affinity for the SSTR subclass 2, particularly including DOTATATE. Many studies have demonstrated the superiority of 68Ga-DOTATATE over conventional imaging, including FDG PET, in detecting sites of disease involvement and have led to guidelines previously recommending against use of FDG PET/CT except in high-grade neuroendocrine carcinoma (NEC), where high FDG uptake is characteristic. However, studies have indicated that FDG-avidity carries an adverse prognosis and can be seen in lower grade NET as well as NEC and can also co-exist with SSTR expression. Therefore, using 68Ga-DOTATATE and FDG can unmask the heterogeneity that exists in this disease, improving lesion sensitivity but also guiding therapy. In particular, FDG-avid lesions that lack SSTR expression are unsuitable for peptide receptor radionuclide therapy (PRRT) and alternative treatments are required to address the adverse prognosis associated with this finding. However, the cost of this imaging paradigm is challenging for many patients and healthcare systems and therefore pragmatic use of these tests requires risk-evaluation and careful consideration of

possible therapeutic options that might be influenced by the result of each test. A case can be made for omitting FDG PET/CT in patients with G1 or G2 NET with stable disease for >6 months or using it as the primary staging investigation in G3 NEC. Use of both tracers could then be reserved for patients with progression over <6 months, irrespective of grade, in the higher end of G2 NET and lower end of G3 NEC or in patients with structural lesions on CT or MRI that lack uptake of the initially chosen tracer. This approach allows rationale treatment choices based on imaging phenotype, while constraining costs and patient inconvenience.

**DR LIAU KUI HIN**
Clinical Director, Nexus Surgical Cancer Centre
Senior Consultant Surgeon, Nexus Surgical Associates
Clinical Senior Lecturer, Yong Loo Lin School of Medicine, National University of Singapore, Singapore

PRESENTATION

# Surgery – Role of Surgery in Management of Metastatic GEP-Nets

The decision for surgical intervention on metastatic GEP-NETs is often not a straight forward deliberation and often is a tricky one. Strong scientific evidence is lacking in guiding the surgeons when to operate and when not to operate. Furthermore, the natural history of GEP-NETs is complex and at times unpredictable. Low grade NETs may turn aggressive unexpectedly and high grade NETs may behave non-aggressively at times. Current biomarkers, at best, help to diagnose and grade the tumours but they are still far from perfect in predicting the natural history of the tumour. This lecture discusses the current practice of surgical oncology in metastatic GEP-NETs focusing on surgical options, the extent of surgery, utility of surgical resections and weighing the survival benefits and symptoms control against the operative and anaesthetic risks.

**DR SHAILESH V. SHRIKHANDE**
Chief, Gastrointestinal and
Hepato-Pancreato-Biliary Service
Professor, Department of Surgical Oncology,
Tata Memorial Centre
Ernest Borges Marg, Parel,
Mumbai, India

PRESENTATION

# Surgical Management of GEP-NEPs - The Tata Memorial Hospital Experience

Neuroendocrine tumors (NET) are rare tumors that have received increasing attention in recent years. The true incidence and prevalence figures in India are not clear though new data is emerging. Tata Memorial Hospital, India's largest tertiary referral cancer centre, has witnessed a dramatic increase in the number of cases treated. This has resulted in the development of dedicated multidisciplinary care for these tumors with involvement of pathologists, medical oncologists, medical gastroenterologists, nuclear medicine specialists, radiologists and specialist surgeons. This lecture provides a detailed analysis of a series of 155 resections (28 from 2005 - 2009 and 127 from 2010 - 2016) for various NET's, the most common being pancreatic resections.

**DR SUGANDHA DUREJA**
Consultant Nuclear Medicine Physician
Department of Nuclear Medicine and Molecular Imaging
Fortis Memorial Research Institute,
Gurgaon, Haryana, India

PRESENTATION

# Theranostics in NETs - From Imaging to Radioguided Surgery and Therapy

THERANOSTICS of neuroendocrine tumors (NETs) is possible by using Gallium-68 labeled tracers for diagnostics with positron emission tomography/computed tomography (PET/CT), and using Lutetium-177, Yttrium 90 or other metallic radionuclides for radionuclide therapy by applying the same peptide targeting the somatostatin receptor overexpression seen in neuroendocrine neoplasms.

Somatostatin receptor PET-CT enables very accurate detection of neuroendocrine tumors and their metastases with high diagnostic sensitivity and specificity and provides quantitative data that can be used for selecting patients for Peptide Receptor Radionuclide Therapy (PRRT) and evaluation of response to therapy. Ga-68 DOTATOC PET has been found to be superior to F-18 FDG PET in the detection of well-differentiated NETs. Therefore molecular imaging and diagnosis of the disease can be effectively followed by personalized treatment.The same somatostatin recetor can be targeted with radiopharmaceuticals for localisation of tumor sites intraoperatively (radioguided surgery) and for therapy.

PRRT is highly effective for the treatment of metastatic grade I and II neuroendocrine neoplasms, and lends a benefit in overall survival by several years. In addition, significant improvement in clinical symptoms and excellent palliation can be achieved. The significant points to take into account concerning PRRT are patient selection, appropriate choice of peptide and radionuclide, renal protection, tumor and organ dosimetry and monitoring of toxicity with regular follow-up. Various newer agents in Theranostics include alpha emitting radionuclides, as well as different somatostatin receptor targets, like somatostatin receptor antagonists.

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PRESENTATION

# Radiotherapy for Lung NETs

Lung NETs are usually treated by surgery for localized disease for systemic therapy for advanced disease. The role of radiotherapy in general has been small. However similar to other advanced cancers, radiotherapy has an important role in palliation of symtoms of metastases such as brain metastases, pain from bone metastases and spinal cord compression. Pressure symptoms from enlarging masses and local symptoms such as haemoptisis can be managed with short courses of focal radiotherapy. Although there are no trials addressing radical radiotherapy for locally advanced disease, curative radiotherapy could be considered for such inoperable disease.

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PRESENTATION

# Management of Non-Secretory Diarrhea

Diarrhea is an extremely frequnet symptom in medical, oncological and gastroenterological patients and has a broad differential diagnosis which requires a structured approach to identfy the correct diagnosis and define appropriate treatment options. In patients with neuroendocrine neoplasias in general and in those with carcinoid syndrome in particular a specific type of diarrhea evoked by uncontrolled hormone secretion (of e.g. serotonin, gastrin or VIP) may cause even life-threatening disturbances with dehydration and electrolyte shifts. However, even in these patients but also NEN-patients with nonfunctional status the differential diagnosis of diarrhea is broad but must be made appropriately. Particularly because insufficient treatment of e.g. infectious causes may lead to insufficient symptom control and clinical decline oft he NEN-patient.

The objective oft he presentation will be discussion of non-hormone hypersecretion-related causes of diarrhea, the impact on intestinal absorptive function and the appropriate diagnostic work-up to achieve a structured step-wise approach to diagnosis and treatment.

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PRESENTATION

# NET G3 – Fact or Fiction

Neuroendocrine neoplasms (NEN) have been classified by the WHO most importantly according to their proliferative capacity which is reflected by Ki67-staining of cell nuclei of cells which will soon undergo cell division. According to this approach, which has been validated in multiple independent cohorts, NEN with a very low proliferative capacity of less than 3% are labelled as neuroendocrine tumors (NET) of grade 1 (G1), if with a proliferative index of 3 to 20% NET G2 and above 20% neuroendocrine carcinomas (NEC) G3. However, it has soon become clear that this classification needs some adaption to real – life tumor biology and NEN oncology. Most importantly it has become clear that the group of so called „NEC" with a proliferative index above 20% is rather heterogenous not just with regard to Ki67-index but with regards to prognosis as well as to responsiveness to treatment. Furthermore, pathologists have noted that beyond immunohistochemical similarities there is heterogeneity among „NEC" with regards to cellular differentiation; in particular, NEN G3 were noted which resemble NET but just „differing" from them by a Ki67-index above 20%. Clinically this specific tumor biology translates into a higher level of somatostatn receptor expression as well as responsiveness to NET- rather than NEC-treatment strategies. According to preliminary remarks a reviewed version of the WHO-classification tob e published in 2017 will likely accept this perspective will lable this subgroup of NEN as NET-G3, by this making it an accepted category and not just a matter of scientific debate.

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PRESENTATION

# Imaging of Neuroendocrine Tumors

Neuroendocrine tumors (NETs) comprise a heterogeneous group of malignancies with variable clinical expression and disease progression. The most common localizations are the lungs, gastrointestinal tract and pancreas. The only curative treatment is surgery, however greater than 50% have metastatic disease at the time of diagnosis. The diagnosis and follow-up of these tumors necessitate a large number of different imaging methods, such as CT, MRI, US, SRS and PET. Ultrasonography offers the possibility to take guided biopsies from different lesions.

| **Technique** | **Applications** | **Organs**[21,26,31,32] | |
|---|---|---|---|
| Computed tomography (CT) | CT can be useful for localizing and staging solid neoplasms, including NETs.[23] It offers good resolution for intrahepatic and extrahepatic metastases, and may help identify bone metastases.[24] | Appendix<br>Colon<br>Duodenum<br>Liver | Rectum<br>Small intestine<br>Stomach |
| Magnetic resonance imaging (MRI) | MRI is an alternative to CT in some cases because neoplasms can be visualized without contrast using T1 and T2 images, reducing the variability sometimes seen on contrast CT.[25] | Colon<br>Duodenum<br>Liver<br>Rectum<br>Stomach | |
| Octreoscan™ (somatostatin receptor scintigraphy) | Octreoscan is a whole-body imaging technique that identifies primary NETs and metastases that express somatostatin receptors.2 It may identify disease sites not previously seen with cross-sectional imaging.[25] Octreoscan is a trademark of Covidien AG or one of its affiliates. | Duodenum<br>Liver<br>Pancreas | |

| Technique | Applications | Organs[21,26,31,32] | |
|---|---|---|---|
| $^{131}$Iodine metaiodobenzylguanidine (MIBG) scintigraphy | MIBG scintigraphy uses injected radioisotope and a specialized scanner to locate and confirm the presence of metastatic pheochromocytoma and neuroblastoma, and certain other NETs.[26-28] | Duodenum<br>Liver<br>Small intestine | |
| Positron emission tomography (PET) | PET may be useful for identifying small NETs. Chemical tracers are used to detect metastases.[4] | Liver<br>Small intestine | |
| Echocardiogram | An echocardiogram can help assess patients for carcinoid heart disease, which occurs in 11% to 66% of patients with carcinoid syndrome.[4,8] | Heart | |
| Endoscopy | Endoscopy can be a valuable tool for the discovery and monitoring of gastrointestinal (GI) NETs.[2] It is not unusual for an asymptomatic NET to be an incidental finding during routine endoscopy.[2] | Rectum<br>Small intestine<br>Stomach | |
| Endoscopic ultrasound (EUS) | EUS is a relatively noninvasive procedure that can be used to detect lesions in the duodenal wall and small lesions in the pancreas.[21,29,30] | Appendix<br>Colon<br>Duodenum<br>Pancreas | Rectum<br>Small intestine<br>Stomach |

**PROFESSOR KJELL OBERG**
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PRESENTATION

# Hallmarks on Neuroendocrine Tumor Development

An important characteristic of cancer cells is their ability to circumvent cellular growth suppression programs, most of which are dependent of the activity of tumor suppressor genes. Several tumor suppressor genes are involved in the pathogenesis of GEP-NETs through evasion of growths suppression. Germline inactivating mutations of the tumor suppressor gene MEN1 are responsible for the majority of familial NETs. Somatic mutations of this genes is present in approximately one third of sporadic foregut NETs. pNETs also occur in Von Hippel Lindau disease which is caused by a mutation in the VHL tumor suppressor gene and in neurofibromatosis (NF1). Inactivating mutations of tumor suppressor genes NF1 and TCS1 plus TCS2 are coding for proteins involved in the negative regulation of the mTOR pathway, a key pathway in the control of cell survival and proliferation. Altered upstream regulators of mTOR (PTEN and TCS2) have been found in sporadic pNETs. The dysfunction of the P53 pathway is another important mechanism contributing to the initiation and progression of pNETs. Although, P53 (TP53 mutations) are rare in NETs, the P53 pathway is commonly altered in pNETs thorough aberrant activation of its negative regulators MDM2, MDM4. TP53 is mostly dysregulated in high grade pNETs. Somatic mutation targeting the cell cycle regulator gene CDKN1B have recently been detected in 8% of small intestinal NETs. The down regulation of other tumor suppressor genes (RASSF1A, CDKN2A, MGMT) by promotor hyper methylation has been reported to be an important event in NET development.

Exomic sequencing of pancreatic NETs has revealed mutations in genes encoding either of the two subunits of the transcription/chromatin remodeling complex consisting of DAXX and ATRX in about 43% of cases. Inactivating mutations of the ATRX or DAXX genes are atypical features of the telomerase independent telomere maintenance mechanism termed alternative lengthening of telomeres (ALT). Targeting ALT could be a therapeutic approach for those patients with pNETs, either alone or in combination with targeting telomerase.

Vascular endothelial growth factor (VEGF) is a key proangiogenic cytokine and crucial for NET carcinogenesis and progression. Patients with NETs have higher levels of circulating VEGF than control subjects and those with progressive disease have higher levels than those with stable disease. Treatment of a utilizing antibody to VEGF (bevacizumab) has been studied in patients with well-differentiated NETs showing clinical activity. Other antiangiogenic substances applied in NETs are tyrosine kinase inhibitors such as sunitinib and pazopanib. G-protein coupled receptor GPCRs have been extensively studied in NETs and stimulation and inhibition of such receptor appears to contribute to sustained tumor growth. The most widely studied are the somatostatin receptors. Glucose-dependent insulinotropic polypeptide (GIP) receptors are expressed in the majority of pancreatic, small bowel and bronchial NETs and might be a target.

The number of mutations in both pNETs and small intestinal NETs are limited compared to other cancers. We need to learn more about the epigenetics of neuroendocrine tumors to understand the drivers of tumor genesis in these tumors. So called molecular (genetic) profiling has just started and it might unveil drugable targets in NETs.

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PRESENTATION

# Immunotherapy – Is It A Valid Alternative For NETs?

Immunotherapy can be defined as a therapeutic intervention that is focused on the immune system, as opposed to the cancer itself. It becomes the patient's own immune response rather than an exogenous drug that acts directly on the disease. This approach to the treatment of cancer is viewed by many as a modern paradigm shift in oncology, in part due to recent successes of immune check point blockade in diverse cancers. The experience with systemic immunotherapy for cancers in prior decades has been more controversial. High dose interlukin 2 meant for renal cell carcinoma and melanoma has led to extremely durable responses but with excessive toxicity.

The first form of immunotherapy for NETs was the introduction of alpha interferon for small intestinal NETs with significant anti-tumor effect in slow growing tumors. The treatment is registered in many countries for treatment of small intestinal NETs and low grade pNETs. Immune check point blockade represent a class of anticancer agents that function by blocking inhibitory immune cell receptors. Among the most important members of this category are monoclonal antibodies that block cytotoxic T lymphocyte associated antigen for CTLA-4 and programed death (PD-1) or its ligand PD-L1. An antigen presenting cell (APC) captures a tumor-associated antigen, it presents a portion of the antigen as a peptide to native T-cells in the context of the so-called immunologic synapse. Both stimulatory and inhibitory signaling between the T-cell and the APC occur at this synapse. By blocking an inhibitory T-cell receptor, that functions in the context is CTLA-4 or PD-L1 will strengthen the immunogenic signal at the APC transmit to the T-cell. Once the T-cell is activated by the APC, it can then encounter malignant cell presenting a cognate peptide and mediate cell lysis. Anti-PD-1 antibodies block this interaction and thus enhance the ability of T-cells to lyse its targeted cell.

The potential for NETs to respond to immune check point inhibitors is not well-known and the immune environment of the NETs remain relatively unexplored. Some recent study aim to look at the expression profile of PD-1, PD-L1 and PD-L2, in both small intestinal NETs and pancreatic NETs. In a recent study of 85 well differentiated NETs (64 SI-NETs, 21 pNETs). Tumoral PD-L1 expression was 0% in SI-NET and 11% in pNET whereas tumoral PD-L2 expression was 88% in SI-NET and 90% in pNET, all these were low grade tumors. PD-1 positive stromal lymphocyte where present in 45%. T-cell infiltrate was more common in pNETs than in SI-NET. Both PD-1 and PD-L1 has been considered markers for possible response of treatment with monoclonal antibody to this antigens. Clinical trials are ongoing, both SI and pNETs.

A new immunotherapy using oncolytic virus, modified adenovirus with a chromogranin A promotor (AdVince) is recently started in a phase I trial. The mechanism is dual with targeting NETs cells, forcing a burst of the cells with a release of substances that will stimulate the immune system, this study will be presented.

In summary, immunotherapy might be a valid alternative to other therapies in NETs. It is important to delineate those tumors which might be more sensitive to this type of treatment. At the moment, it seems to be mostly pNETs and maybe high grade tumors that might be the targets.

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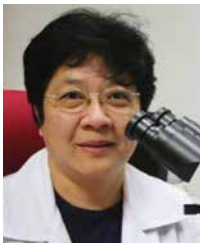

PRESENTATION

# Classification of Gastroentero-Pancreatic Neuroendocrine Tumours (GEP-NETs)

The classification of neuroendocrine tumours (NETs) has been confounded by conceptual difficulties leading to inconsistent terminology and criteria for malignancy. Conceptually, neuroendocrine tumours possess features consistent with an interface between the endocrine (hormonal) and nervous systems, characterised by close relationship to blood sinusoids, ultrastructural exhibition of dense-core secretory granules and expression of amines, peptides and chromogranin. Histopathology may show a range of tumour cell arrangements (polygonal nests, ribbons, glands, isolated cell clusters, signet ring). Immunohistochemical demonstration of neuroendocrine "differentiation" is crucial in its diagnosis. Of these, expression of chromogranin A is the most widely accepted, although synaptophysin and neuron-specific enolase may also be expressed but considered less specific.

Although NETs can occur in almost any organ of the body, gastroentero-pancreatic neuroendocrine tumours (GEP-NETs) are the most prevalent. GEP-NETs have been classified by functionality (insulinoma, glucagonoma) and location (foregut, midgut, hindgut), but the most widely accepted histopathological classification is based on the proliferative rate for grading, and the TNM system for staging. The 2010 WHO classification categorises (1) tumours with a mitotic rate of <2/10hpf or a Ki-67 rate of 2% or less as **Neuroendocrine tumour grade 1**, (2) tumours with a mitotic rate of 2-20/10hpf or a Ki-67 rate of 3-20% as **Neuroendocrine tumour grade 2**, and (3) tumours with a mitotic rate of >20/10hpf or a Ki-67 rate of >20% as **Neuroendocrine tumour carcinoma grade 3**. Grade 3 tumours are further subcategorised into large cell and small cell types. The clinical utility of both grading and staging bears out in their prognostic significance, although further fine-tuning by Ki-67 cut off rates and TNM staging are the subjects of ongoing studies. A fourth category of **Mixed Adenoneuroendocrine Carcinoma (MANEC)** recognises tumours with both adenocarcinoma and neuroendocrine carcinoma components where each component exceeds at least 30% of all neoplastic cells. Scattered neuroendocrine cells (<30%) in adenocarcinomas are not considered MANEC.

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PRESENTATION

# Management of Lung NETs - Surgery

Neuroendocrine tumours (NETS) of the lung represent a distinct subgroup of rare diverse primary lung neoplasms that can be classified into four groups; low grade typical carcinoids, intermediate atypical carcinoids, high grade large cell neuroendocrine carcinoma and small cell lung cancer. The evidence for and role of surgery in the contemporary management of these tumours is presented with an emphasis on surgical techniques and principles.

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IPSEN

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## The Asia Pacific Neuroendocrine Tumour Society (APNETS)

The Asia Pacific Neuroendocrine Tumour Society (APNETS) is a professional society composed of healthcare professionals and scientists with interest in the field of neuroendocrine tumour disease.

APNETS is committed to enhancing the management of neuroendocrine tumours in the Asia Pacific through networking and international collaboration.

Its objectives include:

1. Improving the diagnosis and treatment of neuroendocrine tumours.
2. Supporting and facilitating research on neuroendocrine tumours.
3. Education and training of healthcare professionals through scientific and educational meetings, seminars and workshops.
4. Enhance community awareness on neuroendocrine tumours
5. Development of evidence based consensus guidelines to standardize and improve the management of neuroendocrine tumours.
6. Establishment of an Asia Pacific Neuroendocrine Tumour database and registry.

It was formed in Kuala Lumpur on 7th July 2012 and officially registered on 31st January 2013.

NOTE

NOTE

# HOLD BACK THE PROGRESSION

Somatuline® Autogel® 120 mg is indicated for the treatment of grade 1 and a subset of grade 2 (Ki-67 index up to 10%) gastroenteropancreatic neuroendocrine tumors (GEP-NETs) of mid-gut, pancreatic or of unknown origin where hindgut sites of origin have been excluded, in adult patients with unresectable locally advanced or metastatic disease[1]

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*SSA: Somatostatin analog


1. Somatuline Autogel UK SmPC 2015
2. Caplin M *et al.*, NEJM 2014, 371(3):224-233


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