An approach to NETS

Jose Ramos

University of the Witwatersrand
Donald Gordon Medical Centre
**Epidemiology**

- Incidence appears to be increasing
  - True increase probable
  - Improved imaging
  - Incidental finding
- 90% are sporadic
- 10% arise in MEN1
  - Must exclude MEN – Ca, PTH, gastrin, fasting sugar and insulin, prolactin
- Non-functional vs functional
  - 60% - 90% NF
  - Functional tumours mainly insulinoma and gastrinoma
- All NETs are malignant tumours!
The Overall Incidence of NET Is Increasing Compared With All Malignant Neoplasms

- The incidence and prevalence of NET has increased approximately 500% over the past 30 years which may be partially due to improved diagnosis.

GEPNETs vs Adenocarcinoma

Figure 2: 5 year survival for NETs (A) and gastroenteropancreatic cancers (B)
Gastroenteropancreatic neuroendocrine tumours (GEP NETs) have a significantly better survival than adenocarcinoma at the same location. The 5 year survival of neuroendocrine liver metastases is less than 50%.1

Frilling et al Lancet Oncology Oct 2014
NET Are the Second Most Prevalent Type of Gastrointestinal Malignancy

Prevalence in SEER Database

Standard approach to malignancy

Clinical assessment

Diagnosis

Staging

Treatment
Approach to NET

1. Clinical assessment
2. Diagnosis
3. Grading
4. Staging
5. Treatment
How do we confirm diagnosis and grade?

• FNA adequate for diagnosis in most cases
  • CgA
  • Synaptophysin

• FNA not sufficiently accurate to grade tumours in many cases

• Core biopsy preferred for grading

• Grade of metastases may be higher than that of primary
Grading WHO 2017

- Ki-67
- Mitotic index
- Cell morphology (2017)

PNETs with ki67>20% - Strong evidence that not just ki67/mitotic rate but also morphological differentiation is important.
PNENs and Ki-67
Survival correlates with grading
Relevance of grading

Grade of pancreatic NENs and Ki67-index

- Resection
- Bio-Response-modifiers
- Temozolomide

NET G1: < 2%
NET G2: 2%-20%
NEC G3: > 20%

Probability of survival

Months

No at risk
G1 483 378 280 196 89 33 17 9 4 1
G2 380 278 196 89 33 17 9 4 1
G3 63 15 9 7 1 1 1 0 0 0

95% CI
G1
G2
G3

Rindi et al, JNCI 2012
Staging
Staging of GEP-NENs According to ENETS/WHO/AJCC

**ENETS/AJCC TNM Staging Systems**

<table>
<thead>
<tr>
<th>Stage</th>
<th>T</th>
<th>N</th>
<th>M</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIa</td>
<td>T2</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIb</td>
<td>T3</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIIa</td>
<td>T4</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIIb</td>
<td>Any T</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IV</td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
</tr>
</tbody>
</table>

**ENET/AJCC Classification Criteria – GI NET**

Stage includes tumour location, size, lymph node involvement/distant metastasis

ENETS = European Neuroendocrine Tumour Society
AJCC = American Joint Committee on Cancer

American Joint Committee on Cancer. AJCC Cancer Staging System, 7th ed.
How to stage?

• General
  • CAT scan
  • MRI

• Somatostatin receptor imaging
  • Gallium PET/CT (Dotatate, Dotatoc etc)
    • G1 and low G2
    • Ki-67 < 10%
  • Octreoscan
  • Tektrotyd scan

• FDG PET
  • G2 and G3
  • Ki-67 > 10%
  • Does not depend on SS
  • receptor

Primary and metastases may have different grading
Management
## NET Treatment Options

<table>
<thead>
<tr>
<th>Modality</th>
<th>Disciplines Involved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgical Resection</td>
<td>Surgery</td>
</tr>
<tr>
<td></td>
<td>Anaesthesiology</td>
</tr>
<tr>
<td></td>
<td>Intensive Care</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>Oncology</td>
</tr>
<tr>
<td>Targeted Therapy</td>
<td>Oncology</td>
</tr>
<tr>
<td>Biological Therapy - Somatostatin Analogs (SSA)</td>
<td>Oncology</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>Radiation Therapy</td>
</tr>
<tr>
<td>Ablation – RFA or MWA</td>
<td>Interventional Radiology</td>
</tr>
<tr>
<td>Transarterial embolisation / radioembolisation</td>
<td>Interventional Radiology Radiation Therapy</td>
</tr>
<tr>
<td>Peptide Receptor Radiation Therapy (PRRT)</td>
<td>Nuclear Medicine</td>
</tr>
<tr>
<td>Hormonal control</td>
<td>Endocrinology</td>
</tr>
</tbody>
</table>
A multidisciplinary disease requires a Multi-Disciplinary Team in a Multi-Disciplinary Referral Centre
Management principles

G1/G2

Localised or metastatic

Resectable

Surgery

Unresectable

SSR positive

SSA
PRRT

SSR negative

Everolimus/Sunitinib
Chemotherapy

G3

Chemotherapy
Somatostatin Receptors and Somatostatin Analogs (SSA) in NETs

- More than 90% of NET express somatostatin receptors\(^1\)\(^2\)
  - Somatostatin receptors can be divided into five subtypes, STRs 1-5, based on structure and function
  - In NETs, SSTR2, SSTR5, and SSTR1 are most frequently expressed, followed by SSTR4 and SSTR3\(^3\)
- Somatostatin signaling inhibits secretory and proliferative activity\(^4\); acting on the IGF/PI3K/mTOR pathway\(^5\)
- Octreotide reduces severe diarrhoea and flushing episodes by ≥50% in approximately 74% to 89% of patients with carcinoid syndrome\(^4\)\(^6\)\(^7\)

Somatostatin analogues (SSA) vs PRRT

Netter-1 Trial

\(^{177}\text{Lu-Dotatate} + \text{Octreotide} 30\text{mg/month}\)

vs

\text{Octreotide} 60\text{mg/month}
Using Gallium-PET and FDG-PET to guide treatment

<table>
<thead>
<tr>
<th>Gallium-PET Positive</th>
<th>Gallium-PET Positive</th>
<th>Gallium-PET Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDG-PET Negative</td>
<td>FDG-PET Positive</td>
<td>FDG-PET Positive</td>
</tr>
<tr>
<td>PRRT SSA</td>
<td>PRRT/SSA plus</td>
<td>Everolimus Chemotherapy</td>
</tr>
<tr>
<td></td>
<td>Everolimus/chemotherapy</td>
<td></td>
</tr>
</tbody>
</table>
Summary

• NETs have an increasing incidence and relatively high prevalence
• Survival is dependent on grade and stage of disease
• Grade and stage dictate management
• Surgical resection best treatment for resectable NETs, whether localized or metastatic, if complete resection possible
• Gallium-PET and FDG-PET can be used to guide treatment