SPECTRUM OF NEUROENDOCRINE TUMORS

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Disclosures

• I have no conflicts of interest to disclose.
What is a Neuroendocrine Tumor?

- Heterogenous group of epithelial neoplasms that share a common phenotype — the expression of neuroendocrine differentiation by:
  - Morphologically
  - Electron Microscopy
  - Immunohistochemistry
Morphology

- Nesting, organoid or trabecular growth pattern.
- Coarsely stippled nuclear chromatin ("salt & pepper").
Electron Microscopy

- Dense core neurosecretory granules
  - Membrane bound with narrow halo around the core
  - Vary in size
    - Large and numerous in carcinoid tumors (100-350 nm)
    - Intermediate in WDNC,
    - Small (about 120 nm) and infrequent in pd NET.
Immunohistochemistry

- **Expression of neuroendocrine markers such as:**
  - **Synaptophysin**
    - Most abundant synaptic vesicle membrane glycoprotein in neurosecretory granules
  - **Chromogranin**
    - A secretory protein, located in secretory vesicles of neurons and endocrine cells.
  - **CD56**
    - Glycoprotein expressed on the surface of neurons, glial cells, and numerous hematopoietic cells.
    - Implicated as having a role in cell–cell adhesion and neurite migration
  - **Peptide hormones**
    - Gastrin, insulin, serotonin +
Origin of NET

• These tumors occur in just about every organ in the body.

• Originally these tumors were thought to be derived from embryonic neural crest but this is no longer accepted for all NET.

• Many are of endodermal or ectodermal origin & probably derive from multipotential stem cells.
Origin of Neuroendocrine Cells

- **Ectoderm**
  - Anterior pituitary
  - Merkel Cells (?)

- **Neural Crest**
  - Adrenal medulla
  - Paraganglioma
  - C-cells of thyroid

- **Mesoderm**
  - Adrenal cortex

- **Endoderm**
  - Thyroid
  - Parathyroid
  - Pancreatic islets
  - GI neuroendocrine cells
  - Pulmonary neuroendocrine cells
Classification

• There is still no uniform classification of NET irrespective of site of origin and the terminology for NET is still site specific.
Grading NET

### Table 1. Grading system of gastrointestinal NET

<table>
<thead>
<tr>
<th>Grade</th>
<th>Gep-net (ENETS-WHO 2010)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>&lt;2 mitoses/10HPF AND Ki67 index&lt;3%</td>
</tr>
<tr>
<td>Intermediate</td>
<td>2-20 mitoses/10HPF OR Ki67 index=3-20%</td>
</tr>
<tr>
<td>High</td>
<td>&gt;20 mitoses/10HPF OR Ki67&gt;20%</td>
</tr>
</tbody>
</table>

### Table 2. Grading system of NET of Lung and Thymus

<table>
<thead>
<tr>
<th>Grade</th>
<th>Lung-Thymus (WHO 2004)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>&lt;2 mitoses/10HPF AND No necrosis (Figure 6)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>2-10 mitoses/10HPF OR Foci of necrosis</td>
</tr>
<tr>
<td>High</td>
<td>&gt;10 mitoses/10HPF (Figure 7)</td>
</tr>
</tbody>
</table>

Guadagno et al Front Bioscience Scholar 8:1, 2016
Issues with Ki67 Measurements

• More sensitive than mitotic counts
• Methods of quantification
  – WHO recommends counting 2000 cells (20 fields of 100 cells in most active area)
  – “eyeballing”
  – Image analysis
• Heterogeneity within the tumor
  – How many sections do you stain?
• Discordance with mitotic rate.
Fig. 3 Overall survival of patients with metastatic GEP-NETs stratified by tumor grade.

Fig. 6 Overall survival stratified by the Ki-67 proliferative index (0%-20% versus >20%).

Strosbert et al. Human Pathol 40:1262, 2009
Classification

• In most organs well differentiated NET (Gr 1&2) & poorly differentiated NET are two different families.
  – Only WD NET arise in patients with NE syndromes such as MEN1 or Von Hippel Lindau.
  – PD NET more frequently associated with other elements such as adenoca or SCC.
  – Tumors with combination of WD and PD feature are nearly non-existent
  – Distinct molecular pathways are emerging for WD and PD NET.
Comparison various systems of nomenclature currently in use

<table>
<thead>
<tr>
<th>Grade</th>
<th>Lung and Thymus (WHO)</th>
<th>GEP-NETs (ENETS)²⁸,²⁹</th>
<th>GEP-NETs (WHO 2010)³</th>
<th>Lung and Thymus (Moran et al)²³</th>
<th>Pancreas (Hochwald et al)¹⁴</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low grade</td>
<td>Carcinoid tumor</td>
<td>Neuroendocrine tumor, grade 1 (G1)</td>
<td>Neuroendocrine neoplasm, grade 1</td>
<td>Neuroendocrine carcinoma, grade 1</td>
<td>Well-differentiated pancreatic endocrine neoplasm, low grade</td>
</tr>
<tr>
<td>Intermediate grade</td>
<td>Atypical carcinoid tumor</td>
<td>Neuroendocrine tumor, grade 2 (G2)</td>
<td>Neuroendocrine neoplasm, grade 2</td>
<td>Neuroendocrine carcinoma, grade 2</td>
<td>Well-differentiated pancreatic endocrine neoplasm, intermediate grade</td>
</tr>
<tr>
<td>High grade</td>
<td>Small cell carcinoma</td>
<td>Neuroendocrine carcinoma, grade 3 (G3), small cell carcinoma</td>
<td>Neuroendocrine carcinoma, grade 3, small cell carcinoma</td>
<td>Neuroendocrine carcinoma, grade 3, small cell carcinoma</td>
<td>Poorly differentiated pancreatic endocrine carcinoma, small cell carcinoma</td>
</tr>
<tr>
<td></td>
<td>Large cell neuroendocrine carcinoma</td>
<td>Neuroendocrine carcinoma grade 3 (G3), large cell neuroendocrine</td>
<td>Neuroendocrine carcinoma, grade 3, large cell neuroendocrine carcinoma</td>
<td>Neuroendocrine carcinoma, grade 3, large cell neuroendocrine carcinoma</td>
<td>Poorly differentiated pancreatic endocrine carcinoma, large cell neuroendocrine carcinoma</td>
</tr>
</tbody>
</table>

The grade of the tumor MUST be included in the pathology report, along with a reference to the specific grading system being used. Unqualified terms such as neuroendocrine tumor or neuroendocrine carcinoma without reference to grade do not provide adequate pathology information.

Kimstra et al Pancreas 39:707, 2010
Terminology for Organ Specific Tumors Has Not Changed

- Pheochromocytoma
- Paraganglioma
- Medullary thyroid carcinoma
- Parathyroid adenomas/carcinomas
- Pituitary adenomas/carcinomas
Overview of NET at Different Body Sites

- Pancreas
- GI
  - Stomach
  - Intestines
- Lung
- Thymus
- Genitourinary
  - GYN
  - Prostate
- Skin (Merkels)
- Head and Neck
- Endocrine Organs
  - Thyroid
  - Adrenal
  - Parathyroid
Pancreatic NET

- Most are WD (previously called islet cell tumors) and include an array of functional types (insulinoma, glucagonoma, gastrinoma, VIPoma, somatosatinoma etc) as well as nonfunctional (most common).
Pancreatic NEC

• Compared to other organs the pancreas has more cases that straddle G2/G3 based on mitotic activity and Ki67.

• Concept of WD Gr 3 NEC as distinct entity separate from PD NEC has been proposed.

• PD tumors (small cell or LC NEC) do occur in the pancreas but are rare.
Molecular Alterations in Pancreatic NEC

• Lack changes seen in pancreatic ductal carcinomas (lack mutations in Kras, TP53, CDKN2A or SMAD4).

• Often have alterations in chromatin remodeling genes (MEN1, DAXX, ATRX) as well as alterations of mTOR pathway.
WHO 2010 Classification of NET of the Stomach

- NET Grade 1 (Carcinoid)
- NET Grade 2
- Neuroendocrine Carcinoma
  - Large cell NEC
  - Small cell NEC
- Mixed adenoneuroendocrine carcinoma
- EC cell, serotonin-producing NET
- Gastrin Producing NET (gastrinoma).
Gr1 NET Stomach (Carcinoids)

• **Type 1:** associated with autoimmune chronic atrophic gastritis (usually autoimmune pernicious anemia but sometimes caused by Helicobacter infection.
  – Typically small and multicentric

• **Type 2:** associated with MEN type 1 & Zollinger-Ellison syndrome
  – Associated with hypergastrinemia
  – Typically small and multicentric

• **Type 3:** Sporadic
  – Solitary & associated with gastritis.
Poorly Differentiated NE Carcinomas of Stomach

• Rare and heterogenous group ranging from classic small cell and large cell NEC.

• Often associated with adenocarcinoma components
  – 75% of LG, 55% of SC

• Diffusely positive for at least one conventional neuroendocrine marker (synaptophysin, chromogranin, or CD56).
  – TTF1 expression in 37%

• No difference in survival between pure LG, pure SC and mixed tumors

Intestinal NET

• WD (carcinoid) is a common NET in the terminal ileum.

• Ileum is the most common site for WD NEC associated with carcinoid syndrome.

• PD NEC are rare in the bowel except in patient’s with Crohn’s disease (terminal ileum).
NET of Appendix

Tip of the appendix is a common site for NET

A. Well-differentiated endocrine tumor
   1. Benign behavior
      • Nonfunctioning, and
      • Confined to appendiceal wall, and
      • ≤2 cm, and
      • Nonangioinvasive, and
      • Ki-67 index of ≤2%, and
      • Mitoses of ≤2 cells/high-power fields ×40
   2. Uncertain behavior
      • Nonfunctioning, and
      • Confined to subserosa, or
      • >2 cm, or
      • Angioinvasive

B. Well-differentiated endocrine carcinoma, low-grade, malignant
   • Invading the mesoappendix or beyond, and/or
   • With metastases,
   • With or without a functioning (carcinoid) syndrome

C. Mixed exocrine-endocrine carcinoma
   1. Low-grade, malignant, goblet cell carcinoids

2015 WHO Classification of Pulmonary NET

- Preinvasive pulmonary neuroendocrine lesions
  - Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia
- Typical carcinoid
- Atypical carcinoid
- Small-cell carcinoma—pure and combined
- Large-cell neuroendocrine carcinoma—pure and combined

Travis et al J Thorac Oncol. 10: 1243–1260, 2015
Neuroendocrine Cell Hyperplasia

• Nodular proliferations of neuroendocrine cells
• May be an incidental finding but may present as interstitial lung disease or with multiple pulmonary nodules suggesting metastatic disease.
• Arbitrary size of 4 mm or less suggested for tumorlets -- larger tumors WD NEC
Classic Carcinoid (Grade I Neuroendocrine Tumor)

- Intrabronchial lesions that display trabecular, insular, & solid patterns
- No necrosis
- Less than 2 mitosis per 2 mm²
- Most are sporadic (~2% of primary lung tumors)

Synaptophysin
Chromogranin
Atypical Carcinoid (Grade 2 Neuroendocrine Tumor)

- Currently distinguished by mitotic activity (2-10 MF per 2 mm$^2$) & presence of punctuated necrosis.
- May have more nuclear atypia compared to typical carcinoid.
Small Cell Carcinoma (Grade 3 Neuroendocrine Carcinoma)

- Cells are small (less than the diameter of 3 lymphocytes).
- Arranged in nests, cords or trabeculae
- Nuclear molding
- Fine granular chromatin & inconspicuous nucleoli
- Apoptosis
- Numerous mitosis (usually more than 50 per mm$^2$)
- Necrosis
Large Cell Carcinoma (Grade 3 Neuroendocrine Carcinoma)

- Pleomorphic high grade tumors
  - NE morphology (nesting, organoid, trabecular, palisading)
  - Larger cells with more cytoplasm, numerous mitosis, vesicular chromatin, nucleoli & extensive necrosis.
- Show neuroendocrine differentiation by IHC or EM.

Synaptophysin

Chromogranin
Combined High Grade Neuroendocrine Carcinoma

- Many high grade neuroendocrine carcinomas have overlapping LC and SC features.
- If 10% of the tumor has discordant features - suggested tumor be designated as LC combined type or SC combined type.
Table 2 – Diagnostic criteria for lung neuroendocrine tumors according to WHO 2015 classification.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Typical carcinoid</th>
<th>Atypical carcinoid</th>
<th>Large-cell neuroendocrine carcinoma</th>
<th>Small-cell carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuroendocrine morphology</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Cytologic criteria</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Mitoses/2 mm²</td>
<td>1</td>
<td>2–10</td>
<td>≥11</td>
<td>≥11</td>
</tr>
<tr>
<td>Necrosis</td>
<td>No</td>
<td>Punctate</td>
<td>Extensive</td>
<td>Extensive</td>
</tr>
<tr>
<td>Combined variant</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Ki-67 labeling index</td>
<td>up to 5%</td>
<td>up to 25%</td>
<td>40–80%</td>
<td>50–100%</td>
</tr>
</tbody>
</table>

Carcinoid

Atypical Carcinoid

Small Cell

Large cell
Molecular Changes in Pulmonary Neuroendocrine Carcinomas

Grade I & II
- Relatively few genetic changes.
- Tend to have mutations in chromatin remodeling genes.
  - Mutations in covalent histone modifiers seen in 40%
  - Subunits of the SWI/SNF complex mutated in 22.2%
  - Also mutations in MEN1, PSIP1 and ARID1A
  - TP53 and RB1 mutations are rare (Fernandez-Cuesta et al Nat Commun 5: 3518, 2014).

Grade III
- Frequent mutations in TP53, RB1 and EP300
Thymic NET

• Rare, only 2-5% of thymic tumors
• Classified as with Pulmonary NET
• Carcinoids (WD Grade 1) are rare and most are Atypical Carcinoids (Grade 2) and have an aggressive course.
• Association with MEN1 (25%) & Cushings syndrome is more common than in lung tumors.
• PD NE carcinomas are rare.
Prostate NEC

- Heterogenous group, most associated with the usual prostatic adenocarcinoma
- WD NET (carcinoid) are extremely rare and most have been in young men with MEN syndromes.

Table 1 2016 WHO classification of prostatic neuroendocrine tumors

- Adenocarcinoma with neuroendocrine differentiation
- Adenocarcinoma with Paneth cell-like neuroendocrine differentiation
- Well-differentiated neuroendocrine tumor (carcinoid tumor)
- Small cell neuroendocrine carcinoma
- Large cell neuroendocrine carcinoma

Priemer et al Endocr Pathol 2/17/16
Prostate Small Cell Neuroendocrine Carcinoma

- Most are transdifferentiation of usual prostate adenocarcinoma (most have high grade Gleason’s 4/5)
Prostate Small Cell Neuroendocrine Carcinoma

- IHC
  - Synapto and chromo positive
  - Small cell component usually negative for Prostate markers (PSA)
  - Many are TTF1 pos
- 50% of small cell carcinomas of prostate have ERG/TMPRSS2 translocations.
- Tends to occur with androgen resistance
Prostate Large Cell Neuroendocrine Carcinoma

- Rare, tends to have large cells with abundant cytoplasm, coarse chromatin, nucleoli.
- Pos strong IHC staining with at least one NE marker and minimal staining PSA or PAP
- Most associated with prior androgen therapy
GYN Neuroendocrine Tumors
Ovarian Tumor in 15 yr old girl
Small Cell Carcinoma of Ovary
Hypercacinemic type

- Aggressive ovarian tumor of young women (average age of 23, range 9-43 yrs)
- Most common undifferentiated ovarian tumor in women under 40
- 99% are unilateral but at dx over 50% of patients have extraovarian spread
- About 2/3 patients have elevated serum calcium at presentation, but rarely clinically manifested.
Cervical Small Cell Carcinoma

- Synapto
- P16
- TTF1
HPV in Cx Small Cell Ca

**TABLE 1.** HPV mRNA expression in 20 small-cell cervical carcinomas

<table>
<thead>
<tr>
<th>Neuroendocrine markers</th>
<th>HPV type</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>16</td>
<td>18</td>
<td>Neg</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>NSE</td>
<td>5</td>
<td>0</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>NSE &amp; CH</td>
<td>8</td>
<td>1</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>NSE &amp; CH &amp; SYN</td>
<td>5</td>
<td>0</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>20</td>
<td>3</td>
<td>14</td>
<td>3</td>
</tr>
</tbody>
</table>

HPV, human papillomavirus; mRNA, messenger RNA; NSE, neuron-specific enolase; CH, chromogranin; SYN, synaptophysin.

**Table 1.** Correlation Between Human Papillomavirus Infection and Histologic Subtype: Human Papillomavirus Expression in 25 Small Cell Carcinomas of the Cervix

<table>
<thead>
<tr>
<th>HPV-16</th>
<th>HPV-18</th>
<th>Negative</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCC</td>
<td>4</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>SCC + SqCC</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>SCC + ACC</td>
<td>1</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>7 (28%)</td>
<td>10 (40%)</td>
<td>8 (32%)</td>
</tr>
</tbody>
</table>

SCC: small cell carcinoma; HPV: human papilloma virus; SqCC: squamous cell carcinoma; AC: adenocarcinoma.

  - 20 Cases
  - In situ Hybridization
  - 17 positive (85%)

- **Abeler et al Cancer 73:672, 1994**
  - 25 cases
  - In situ hybridization
  - 17 positive (68%)
NE Carcinomas of Head & Neck
Some HPV related

- Small cell Carcinoma of oropharynx (9 cases)
  - 5 HPV 16 pos by ISH

- Large cell Neuroendocrine Carcinoma of H&N (10 cases).
  - 3 HPV pos by ISH
Viral Etiology for HG Neuroendocrine Ca

- Cervix – HG NEC – HPV
- Oropharynx – HG NEC -- HPV
- Skin -- Merkel Cell – polyoma virus
Skin: Merkel Cell Ca
Merkel Cell Carcinoma

- Primary neuroendocrine tumor of the skin
- Rare (0.45 cases per 100,000) Incidence increased 3x between 1986 and 2001.
- Usually in elderly
  - 69 average age at presentation
- Risk Factors:
  - Immunosuppression
  - Male
  - Fair skin
- Most common H&N, extremities (usually sun exposed skin)
- Aggressive (5 yr survival 30-75%)
Merkel Cell Carcinoma

Merkel Cells are found associated with touch receptors (Haarsheiben domes) & release glutamate to juxtaposed sensory nerves in response to pressure stimulation.
CANCER

A Skin Cancer Virus?

Raphael P. Viscidi¹ and Keerti V. Shah²

Is there a virus that causes Merkel cell carcinoma, a rare but aggressive skin cancer? Maybe. On page 1096 in this issue, Feng et al. (1) describe Merkel cell polyomavirus, a new human virus that is associated with a particular neuroectodermal skin cancer that occurs primarily in elderly immunosuppressed individuals. It may be the first example of a human cancer caused by a polyomavirus, a viral family whose association to other cancers has been controversial.

Human polyomaviruses BKPyV and JCPyV were discovered in 1971, and are common infections of the urinary tract, responsible, respectively, for nephropathy in kidney-transplant recipients and progressive multifocal leukoencephalopathy in immunosuppressed populations. Both viruses are widespread and persist as latent infections without causing disease.

Phylogenetic analysis reveals deep evolutionary relationships among the mammalian polyomaviruses (see the figure) (4), and supports the existence of four clades represented by mouse, bovine, and simian/human polyomaviruses (which includes BKPyV and JCPyV), and a separate clade formed by the newly discovered KIPyV and WUPyV. The latter three are sister clades that share a common ancestor, and are distantly related to the mouse polyomavirus clade. Phylogenetically, Merkel cell polyomavirus falls within the mouse polyoma clade and is most closely related to the lymphotropic polyomavirus (also known as African green monkey polyomavirus) of presumed simian origin. Polyomaviruses are highly species-specific and are believed to evolve in close association with their host. The evolutionary position of Merkel cell polyomavirus calls into question this

High-throughput DNA sequencing has identified a new human virus in a rare but aggressive form of skin cancer.

Polymaviruses. A schematic representation of the evolutionary relationships among the animal and mammalian polyomaviruses. KI, WU, JC, BK, and Merkel cell polyomaviruses infect humans. (Inset) Merkel cell carcinoma, cytokeratin 20 staining; magnification ×40 (1).

Merkel Cell Polyomavirus was detected in 8 of 10 MCC samples by Southern Blot. Viral DNA clonally integrated in 6 of 8 tumors.

Familial Syndromes Associated with NET

- **MEN1**
  - NET of parathyroid, pituitary, pancreas, duodenum, carcinoids
  - Inactivation of MEN-1 which encodes for menin protein (80% truncation mutations)
  - Menin is involved in binding to multiple protein partners (at least 25 known) including transcription factors, DNA repair proteins

- **MEN2**
  - Medullary carcinoma of thyroid and some pheochromocytoma
  - Activating mutations of RET proto oncogene, a transmembrane tyrosine kinase which activates the P13K/AKT and RAS/Raf/MAPK dependent cell signaling
  - Pheochromocytomas associated with RET mutation in codon 11
Familial Syndromes Associated with NET

- **Von Hippel Lindau**
  - RCC most common but also
    - Pancreas NET
    - Pheochromocytomas
    - Paragangliomas
    - Hemangioblastoma
  - Germline mutations in VHL tumor suppressor gene (3p25-26)

- **Neurofibromatosis**
  - 5% develop catecholamine producing tumors (pheochromocytomas and paragangliomas)

- **Tuberosclerosis**
  - Pancreatic NET.
## Some Molecular Alterations in NET

<table>
<thead>
<tr>
<th>NET</th>
<th>Molecular Alterations Identified</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancreatic NET</td>
<td>-Alterations in chromatin remodeling genes (MEN1, DAXX, ATRX)</td>
</tr>
<tr>
<td></td>
<td>-Alterations in mTOR pathway (loss of function mutations in TSC1 and TSC2 genes that inhibit mTOR in ~15%).</td>
</tr>
<tr>
<td>Lung carcinoids (Gr1&amp;2)</td>
<td>Mutations in histone modifiers, MEN1, PSIP1, SW1/SNF complexes</td>
</tr>
<tr>
<td>Lung LC &amp; SCC</td>
<td>Mutations in PT53, RB1</td>
</tr>
<tr>
<td>Prostate SCC</td>
<td>ERG/TMPRSS2 translocations &amp; amplification of androgen receptors, AURA &amp; myc.</td>
</tr>
<tr>
<td>SCC cervix</td>
<td>HPV</td>
</tr>
<tr>
<td>LC&amp;SC H&amp;N</td>
<td>HPV</td>
</tr>
<tr>
<td>Merkel Cell</td>
<td>Polyoma</td>
</tr>
</tbody>
</table>
Pathologic Reporting of NET

- Site of the tumor
- Size (3 dimension)
- Presence of unusual histologic features (clear cells, Oncocytic cells etc).
- Grade
  - Mitotic Count (number per 2 mm²) Count 50 fields
  - Ki67 (WHO suggests 2000 cells in most active area)

Klimstra et al AM J Surg Path 34:300, 2010
Pathologic Reporting of NET

- Presence or absence of necrosis
- Invasion (AJCC) landmarks for analogous carcinomas at same anatomic site.
- LVS
- Lymph Node involvement
- Margins

Klimstra et al AM J Surg Path 34:300, 2010
Neuroendocrine Tumors

Very diverse group of tumors in terms of origin, histologic patterns, molecular alterations, and behavior.