NET / GIST / MEN

2014/2015 FCDS Educational Webcast Series

October 16, 2014
Steven Peace, CTR

Anatomy and Physiology of the (Neuro)Endocrine System
WHO Classification, Tumor Grade, Hereditary Syndromes
Signs & Symptoms, Hormone Regulation and Tumor Markers
CSv02.05 and SSFs, AJCC TNM 7th ed, SS2000
Plus...NCCN Treatment Guidelines

Sponsorship

The Florida Cancer Data System sincerely thanks the Florida Department of Health, the Centers for Disease Control and Prevention National Program of Cancer Registries, and the University of Miami Miller School of Medicine for their support.
Presentation Outline

- The (Neuro)Endocrine System – Anatomy & Physiology
  - Hormone Regulation - Form and Function
  - Hereditary Syndromes
- The GI Tract - Relationship with NET and GIST Tumors
- WHO Classification for NET, GIST and Endocrine Tumors
- Mitotic Rate and Tumor Grade
- Signs and Symptoms
- Tumor Markers
- Staging NET and GIST Tumors
- NCCN Treatment Guidelines

What is the “Stroma” of an Organ?

- **DEFINITION:** “Stroma” is the supportive framework of an organ, gland or other structure that is usually composed of connective tissue. The stroma is distinct from the “parenchyma”, which is the of the key functional tissue or elements of that organ that makes the organ, gland or structure do what is intended to do. It holds things together.

- **Stroma/Connective Tissue Includes:** soft tissue, muscle, bone, tendons, mesentery, fibrous tissue, fatty tissue, lymphatic tissue, subcutaneous tissue, blood vessels, lymph vessels, and even nervous system tissues that lie outside the brain and CNS (autonomic and peripheral nervous systems), and even the tissues of the pleural cavity, peritoneum and retroperitoneum including the omentum and mesentery.
The endocrine system works alongside of the nervous system to form the control systems of the body. The nervous system provides a very fast and narrowly targeted system to turn on specific glands and muscles throughout the body. The endocrine system, on the other hand, is much slower acting, but has very widespread, long lasting, and powerful effects. Hormones are distributed by glands through the bloodstream to the entire body, affecting any cell with a receptor for a particular hormone. Most hormones affect cells in several organs or throughout the entire body, leading to many diverse and powerful responses.
Autonomic Nervous System

The Endocrine System - A&P
The (Neuro)Endocrine System - A&P

- The (Neuro)Endocrine System includes the Endocrine System (glands and organs) **PLUS** the Diffuse Neuroendocrine System
- The Diffuse Neuroendocrine System or Diffuse NES is made up of scattered neuroendocrine cells distributed throughout the body - each location serving different function - no organ/gland
- **Diffuse NES Examples:**
  - Digestive NES cells - regulate release of digestive enzymes
  - Digestive NES cells - regulate intestinal movements
  - Respiratory NES cells - regulate respiratory function
  - Adrenal Medulla and Paraganglia (organ) - regulate blood pressure and heart rate - produce both epinephrine and neuro-epinephrine
  - Neuroendocrine cells are also found in non-neuroendocrine glands
  - Neuroendocrine cells are also diffusely scattered in skin, thymus, prostate, and other glands and tissues
  - Pancreatic Islet Cells of the Pancreas Gland – Islets of Langerhans – produce insulin to regulate sugar levels in the body and bloodstream
Neuroendocrine Tumors - NET

- Neuroendocrine Tumors or NETs are often referred to by a different names – some of this is historical – some habit.
- Many NETs are benign tumors but some highly malignant.
- Neuroendocrine Tumors known widely by another name:
  - Merkel Cell Carcinoma
  - Medullary Thyroid Carcinoma
  - Carcinoid Tumor (low-grade NET)
  - Pheochromocytoma/Paraganglioma
  - PanNET – Pancreatic Neuroendocrine Tumor
  - Poorly Differentiated Large Cell Carcinoma (high-grade NET)
  - Poorly Differentiated Small Cell Carcinoma (high-grade NET)
  - ACTH-dependent or ACTH-independent Cushing Syndrome
- Mitotic Index, Ki-67 Index, Hormone Functionality - Indicators

NETs that are NOT this Type of NET

- Today’s Webcast NETs are NeuroENDOCRINE Tumors
- NeuroECTODERMAL Tumors are also called NETs
- This type of NET includes rare pediatric brain tumors and Ewing Sarcoma that develop from undeveloped and/or non-differentiated embryonal neural tissue of the ectoderm or tissues that become brain and CNS.
  - CNS PNET – primitive neuroectodermal tumor of CNS
  - PPNET – peripheral primitive neuroectodermal tumor – Ewing’s
- DNET – dysembryoplastic neuroepithelial tumor and not related to other NETs noted above.
Hormone Regulation - Form & Function

**SERUM HORMONE EVALUATION POTENTIALLY INDICATED IN THE WORKUP OF NEUROENDOCRINE TUMORS**

**HORMONE-RELATED STUDIES (blood markers)**

- Carcinoid tumors
  - 5-HIAA (24-hour urine)
  - Chromogranin A (category 3)
  - PanNET
  - Chromogranin A (category 3)
  - Gastrinoma
  - Insulinoma
  - Proinsulin
  - Insulin/glucose ratio
  - C-peptide
  - VIPoma
  - VIP
  - Glucagonoma
  - Glucagon
  - Blood glucose
  - CBC
  - Other pancreas
  - Somatostatin
  - Pancreatic polypeptide
  - Calcitonin
  - PTH-related peptide

- Pheochromocytoma/paraganglioma
  - Metanephrines (plasma and urine)
  - Pituatory
  - Growth hormone/IGF-1
  - Prolactin
  - LH/FSH
  - TSH
  - Alpha subunits
  - ACTH
  - Ectopic hormones
  - ACTH
  - GRH
  - GHRH

Source: www.nccn.org/neuroendocrine.pdf

---

**Hormone Regulation - Form & Function**

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Origin</th>
<th>Hormone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carcinoid</td>
<td>Enterochromaffin Cells Digestive Tract and Lungs</td>
<td>Serotonin Tachykinins, Histamine Kallikrein</td>
</tr>
<tr>
<td>Pancreatic Neuroendocrine</td>
<td>Islet Cells Pancreas</td>
<td>Gastrin, Insulin, Glucagon, VIP, Somatostatin, PTH</td>
</tr>
<tr>
<td>Medullary Thyroid</td>
<td>Parafollicular (C-cells) Thyroid</td>
<td>Calcitonin</td>
</tr>
<tr>
<td>Pheochromocytoma</td>
<td>Adrenal Medulla</td>
<td>Epinephrine, Norepinephrine</td>
</tr>
</tbody>
</table>

What is a “Functional” Tumor?

“Functional” Neuroendocrine Tumors are NETs that produce an excess of hormones that can lead to a variety of hormone-related symptoms including facial or body flushing, diarrhea or bronchospasms. Over the long-term the chronic over/under expression of hormones can lead to other life-threatening conditions such as carcinoid heart disease – fibrous heart & valves, diabetes, weight gain, diarrhea, sudden growth of hands or feet, etc.

Examples of “Functional” Hormone-Producing NETs

- **Insulinoma** – tumor produces excess/insufficient insulin
- **Glucagonoma** – interferes with production of glucose which then causes problems with high blood sugar and worsening diabetes
- **Gastrinoma** – increased production of gastrin leading to ulcers
- **Somatostatinoma** – disrupts multiple hormone balances leading to diabetes, gallstones, and inability to digest fats
- **VIP-oma** – disrupts vasoactive intestinal peptide – severe diarrhea
- **GRF-oma** – produce excessive amounts of growth hormone release factors – leads to sudden growth of feet and hands
- **ACTH-oma** – produce excessive amounts of the hormone ACTH. Too much ACTH increased production of steroids which lead to weight gain, depression, increased risk of infection, skin changes.
Hereditary Syndromes - NET

Rare Genetic Disorders at Increased Risk of NETs

- MEN 1 – Multiple Endocrine Neoplasia Type 1
- MEN 2 – Multiple Endocrine Neoplasia Type 2
- Von Hippel-Lindau Syndrome
- Tuberous Sclerosis
- Neurofibromatosis Type 1 (von Recklinghausen Disease)

Hereditary Syndromes - GIST

Carney-Stratakis Syndrome

Carney-Stratakis syndrome is a recently described familial syndrome characterized by gastrointestinal stromal tumors (GIST) and paragangliomas, often at multiple sites. It is a very rare syndrome reported in less than 20 unrelated families to date. It presents at a young age (median age: 19 years) with an apparently equal ratio of male and female patients. Patients with Carney-Stratakis syndrome have both GIST and paraganglioma. The gastric stromal sarcomas are multifocal and the paragangliomas are multicentric.
The GI Tract – NETs & GISTs

- NETs in the GI Tract develop in the neuroendocrine cells of the connective tissues in and around the GI Tract and may grow inward or outward. NETs in the GI Tract stimulate hormone-producing endocrine cells resulting in the overproduction of vasoactive peptide hormones (serotonin (5-HT), histamines and tachykinins) causing a constellation of symptoms – “carcinoid syndrome” – causing flushing, fatty diarrhea, bronchospasms, and “dumping” syndrome.

- GISTs in the GI Tract develop in the muscle layer of the walls of the GI Tract from the esophagus down to the rectum and grow outward. GIST do not cause symptoms in early stages. Symptoms can include nausea, vomiting, weight loss, pain, and bleeding. Early tumors are usually incidental findings. They make up only about 1% of all GI Tract neoplasms.

Source: www.executivetravel.com
The GI Tract - GIST

- GIST originate in the interstitial cells of Cajal of the GI Tract.
- The cells create neurotransmitter type impulses that contract smooth muscle along the GI Tract to regulate peristalsis - pushing materials down the digestive tract.
- GIST do not effect hormone function, production or release.
- GIST can occur in the esophagus, stomach, small intestine, appendix, colon, rectum, and in parts of the peritoneum.
- When no primary is stated, the site is coded GI Tract, NOS.

WHO Classification – GIST

- Historical Names
  - GANT
  - Gastric Leiomyoma
  - GI Tract Leiomyosarcoma
  - GI Tract Leiomyoblastoma

- Current Definition - GI tract associated mesenchymal neoplasm with activating mutation in KIT (CD117) or platelet derived growth factor A (PDGFRA)
Only 35%-50% of all GIST are classified as malignant.

**ALL GIST HAVE MALIGNANT POTENTIAL.**

Location, Size, and Mitotic Index are Key Indicators.

**Site Distribution in the GI Tract:**
- 60% - Stomach
- 30% - Small Intestine
- 3% - Rectum
- 1-2% Colon
- 1% Esophagus
- Rare - Omentum/Mesentery

## WHO Classification – GIST

**Risk Stratification of Primary GIST by Mitotic Index, Tumor Size, and Tumor Location**

<table>
<thead>
<tr>
<th>Mitotic Index, hpf</th>
<th>Size, cm</th>
<th>Site and Risk of Progressive Disease (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤5 per 50</td>
<td>≤2</td>
<td>None (0)</td>
</tr>
<tr>
<td></td>
<td>&gt;2 ≤5</td>
<td>Very low (1.9)</td>
</tr>
<tr>
<td></td>
<td>&gt;5 ≤10</td>
<td>Low (3.6)</td>
</tr>
<tr>
<td></td>
<td>&gt;10</td>
<td>Moderate (10)</td>
</tr>
<tr>
<td>&gt;5 per 50</td>
<td>≤2</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>&gt;2 ≤5</td>
<td>Moderate (16)</td>
</tr>
<tr>
<td></td>
<td>&gt;5 ≤10</td>
<td>High (55)</td>
</tr>
<tr>
<td></td>
<td>&gt;10</td>
<td>High (86)</td>
</tr>
</tbody>
</table>

Source: [www.cancer.gov/cancertopics/pdq/treatment/gist](www.cancer.gov/cancertopics/pdq/treatment/gist)

## WHO Classification – Endocrine

- **Endocrine Neoplasms are tumors of Endocrine Organs**
  - Pancreas
  - Testis
  - Ovaries
- **Endocrine Neoplasms are tumors of Endocrine Glands**
  - Pineal Gland
  - Pituitary Gland
  - Adrenal Gland
  - Thyroid Gland
  - Thymus Gland
  - Adrenal Glands
  - Parathyroid Glands
- **Endocrine Neoplasms are not necessarily NETs**
Tumors that arise in the Diffuse Neuroendocrine System

- REPEAT: The Diffuse Neuroendocrine System or Diffuse NES is made up of scattered neuroendocrine cells distributed throughout the body - each location serving different function - no organ/gland - and rare neoplasms.
  - Merkel Cell Carcinoma
  - Medullary Thyroid Carcinoma
  - Carcinoid Tumor (low-grade NET)
  - Pheochromocytoma/Paraganglioma
  - PanNET - Pancreatic Neuroendocrine Tumor
  - Poorly Differentiated Large Cell Carcinoma (high-grade NET) - not lung
  - Poorly Differentiated Small Cell Carcinoma (high-grade NET) - not lung
  - ACTH-dependent or ACTH-independent Cushing Syndrome

- Mitotic Index, Ki-67 Index, Hormone Functionality - Indicators

**WHO Classification – NET**

**Mitotic Rate (Index) and Grade – NET**

### Mitotic Rate

- Mitotic rate should be based upon counting mitoses in at least 40 fields at 40x magnification in the areas of highest mitotic density, and should be reported as the number of mitoses per 10 HPF or per 2 mm². Ten HPF is equivalent to 2 mm² on many microscopes, although the field size may vary slightly.
- Note that in cases where an accurate mitotic rate is precluded by inadequate tissue, such as in small biopsy samples including FNA, the Ki-67 index is the preferred method of establishing the proliferative rate.

### Ki-67 Index

- Ki-67 index is reported as the percentage of positive tumor cells in the area of highest nuclear labeling. Although recommendations have been to count 1000 tumor cells in order to determine the Ki-67 index, this is not practical in routine clinical practice. It is therefore currently acceptable to estimate the labeling index, despite the recognition that estimation is subject to limitations in reproducibility.
- If both mitotic rate and Ki-67 index are used and these are discordant, it is currently recommended that the higher grade be used to assign classification.

### Table 1

<table>
<thead>
<tr>
<th>Grade</th>
<th>Gastroenteropancreatic (GEP) NETs</th>
<th>Lung and Thymus</th>
<th>Differentiation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Grade (G1)</td>
<td>&lt;2 mitoses/10 HPF AND/OR &lt;3% Ki-67 index</td>
<td>&lt;2 mitoses/10 HPF AND/OCC no necrosis</td>
<td>Well-differentiated NET</td>
</tr>
<tr>
<td>Intermediate Grade (G2)</td>
<td>2-20 mitoses/10 HPF AND/OR 3-20% Ki-67 index</td>
<td>2-10 mitoses/10 HPF AND/OR foc of necrosis</td>
<td>Well-differentiated NET</td>
</tr>
<tr>
<td>High Grade (G3)</td>
<td>&gt;20 mitoses/10 HPF AND/OR &gt;20% Ki-67 index</td>
<td>&gt;10 mitoses/10 HPF</td>
<td>Poorly differentiated neuroendocrine carcinoma</td>
</tr>
</tbody>
</table>


Table 1 should be used as a general guide. Definitions vary between lung, thymus, and GEP-NETs in some classification systems. It is recognized that occasionally a morphologically "well-differentiated" NET may have a proliferation index by Ki-67, which technically falls into the "high-grade" category by this measure alone. Clinical judgment should be used in such discordant cases. In general, this discordance should not cause a reclassification of a well-differentiated high-grade NET. In practice, such a distinction is subjective and may depend on the use of specific immunohistochemical markers in lung and thymus with the specific mitotic rate and Ki-67 proliferation index included in the report as additional information. (See NE_A2.4 of 6)

Source: www.nccn.org/neuroendocrine.pdf
# Mitotic Rate (Index) and Grade – GIST

<table>
<thead>
<tr>
<th>Grade</th>
<th>Mitotic rate</th>
<th>Number of mitoses per 50 high-power fields (HPF)</th>
</tr>
</thead>
<tbody>
<tr>
<td>low</td>
<td>low</td>
<td>less than 5</td>
</tr>
<tr>
<td>high</td>
<td>high</td>
<td>more than 5</td>
</tr>
</tbody>
</table>

## DOES MITOTIC RATE (INDEX) EFFECT STAGE?

- **YES** -

---

### Mitotic Rate and TNM Stage – GIST

<table>
<thead>
<tr>
<th>TNM Stage</th>
<th>TNM</th>
<th>Mitotic Rate</th>
<th>Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>stage IA</td>
<td>T1, T2 N0 M0</td>
<td>low</td>
<td>The tumour is no bigger than 5 cm in diameter. The cancer has not spread to nearby lymph nodes or distant sites. The mitotic rate is low.</td>
</tr>
<tr>
<td>stage IB</td>
<td>T3 N0 M0</td>
<td>low</td>
<td>The tumour is bigger than 5 cm, but not bigger than 10 cm. The cancer has not spread to nearby lymph nodes or distant sites. The mitotic rate is low.</td>
</tr>
<tr>
<td>stage II</td>
<td>T1, T2 N0 M0</td>
<td>high</td>
<td>The tumour is no bigger than 5 cm in diameter. The cancer has not spread to nearby lymph nodes or distant sites. The mitotic rate is high.</td>
</tr>
<tr>
<td></td>
<td>T4 N0 M0</td>
<td>low</td>
<td>The tumour is bigger than 10 cm. The cancer has not spread to nearby lymph nodes or distant sites. The mitotic rate is low.</td>
</tr>
<tr>
<td>stage IIIA</td>
<td>T3 N0 M0</td>
<td>high</td>
<td>The tumour is bigger than 5 cm, but not bigger than 10 cm. The cancer has not spread to nearby lymph nodes or distant sites. The mitotic rate is high.</td>
</tr>
<tr>
<td>stage IIIB</td>
<td>T4 N0 M0</td>
<td>high</td>
<td>The tumour is bigger than 10 cm. The cancer has not spread to nearby lymph nodes or distant sites. The mitotic rate is high.</td>
</tr>
<tr>
<td>stage IV</td>
<td>any T N1 M0</td>
<td>any rate</td>
<td>The tumour is any size. The cancer may or may not have spread to nearby lymph nodes. The cancer has spread to distant sites. The tumour has any mitotic rate.</td>
</tr>
<tr>
<td></td>
<td>any T any N M1</td>
<td>any rate</td>
<td>The tumour is any size. The cancer may or may not have spread to nearby lymph nodes. The cancer has spread to distant sites. The tumour has any mitotic rate.</td>
</tr>
</tbody>
</table>
Signs and Symptoms

- Pain
- Asthma
- Diabetes
- Gallstones
- Stomach ulcers
- Severe diarrhea
- Sudden food allergies
- Facial or body “flushing”
- Anxiety and/or Depression
- Other functional bowel disease
- Hypoglycemia (low blood sugar)
- Sudden growth of the hands and feet (acromegaly)

Source: www.mja.com.au/Volume 193 Number 1

Tumor Markers - NET

- **CgA or Chromogranin** – Most Important NET Marker
  - Elevated in 60%-80% of functional and non-functional NETs
- **5-HIAA – 5-hydroxyindoleacetic acid**
  - A product of the breakdown of serotonin
- **Excess Hormone Levels in Blood**
  - Human Growth Hormone
  - Glucocorticoid Steroids
  - Somatostatin
  - Serotonin
  - Insulin
  - Gastrin
  - ACTH
**Tumor Markers - NET**

Utility of chromogranin A (CgA) as a marker of neuroendocrine tumours (NETs)

Source: www.mja.com.au/Volume 193 Number 1

---

**Somatostatin Receptors and Octreotide**

<table>
<thead>
<tr>
<th>Neoplasm</th>
<th>In vivo</th>
<th>Ant 4 hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>GH-producing pituitary tumour</td>
<td>7/10 70%</td>
<td></td>
</tr>
<tr>
<td>TSH-producing pituitary tumour</td>
<td>2/2 100%</td>
<td></td>
</tr>
<tr>
<td>Non-functioning pituitary tumour</td>
<td>12/16 75%</td>
<td></td>
</tr>
<tr>
<td>Gastrinoma</td>
<td>12/12 100%</td>
<td></td>
</tr>
<tr>
<td>Insulinoma</td>
<td>14/23 61%</td>
<td></td>
</tr>
<tr>
<td>Glucagonoma</td>
<td>3/3 100%</td>
<td></td>
</tr>
<tr>
<td>Unclassified APUDoma</td>
<td>16/16 98%</td>
<td></td>
</tr>
<tr>
<td>Paraganglioma</td>
<td>33/33 100%</td>
<td></td>
</tr>
<tr>
<td>Medullary thyroid carcinoma</td>
<td>10/10 71%</td>
<td></td>
</tr>
<tr>
<td>Neuroblastoma</td>
<td>8/9 89%</td>
<td></td>
</tr>
<tr>
<td>Pheochromocytoma</td>
<td>12/14 86%</td>
<td></td>
</tr>
<tr>
<td>Carcinoid</td>
<td>69/72 96%</td>
<td></td>
</tr>
<tr>
<td>Small cell lung cancer</td>
<td>34/34 100%</td>
<td></td>
</tr>
</tbody>
</table>

Source: www.med.harvard.edu
Multiple Primary Rules

- Use Site of Origin for First Line MPH Rules
- Use Other Sites as Last Resort for MPH Rules
- Currently No Specific Set of Rules for NET or for GIST or any other Endocrine Neoplasms.

Histology – Code the Most Specific Histology
- Neuroendocrine Carcinoma is an NOS term
- Carcinoid Tumor is more specific
- Mucinous Carcinoid Tumor is most specific

Source: SEER Summary Staging Manual 2000

SS2000 last updated in 2000
SS2000 is NOT consistent with TNM or CS Schema

Source: SEER Summary Staging Manual 2000
Staging NET Neoplasms

- Use Specific CS Schema or TNM Chapter
  - NET Ampulla
  - NET Colon
  - NET Rectum
  - NET Small Intestine
  - NET Stomach

- If no Specific CS Schema or TNM Chapter
  - Use the Site/Organ/Organ System of Origin to stage

- If no Organ of Origin is noted – C80.9

---

Note 1: Ignore intraluminal extension to adjacent segment(s) of colon/rectum or to the ileum from the cecum; code depth of invasion or extracolonic spread as indicated.

Note 2: AJCC does not include a Tis category for Neuroendocrine Tumors (NET) of the colon. CS Extension code 000 is mapped to TX for AJCC stage and in situ Summary Stage.

Note 3: The assignment of the T categories for NETs of the colon/rectum is based on tumor size and extension. A physician’s statement of the T category may be used to code both CS Tumor Size and/or CS Extension if this is the only information in the medical record regarding one or both of these fields. However the two fields are coded independently; for example, the record may document size but not extension.
**Staging NET Neoplasms**

<table>
<thead>
<tr>
<th>Node</th>
<th>Staging Information</th>
<th>T1</th>
<th>T2</th>
<th>T3</th>
</tr>
</thead>
<tbody>
<tr>
<td>170</td>
<td>Stated as T1a with no other information on extension</td>
<td>^</td>
<td>L</td>
<td>L</td>
</tr>
<tr>
<td>180</td>
<td>Stated as T1b with no other information on extension</td>
<td>^</td>
<td>L</td>
<td>L</td>
</tr>
<tr>
<td>190</td>
<td>Stated as T1 (NOS) with no other information on expansion</td>
<td>^</td>
<td>L</td>
<td>L</td>
</tr>
<tr>
<td>200</td>
<td>Muscularis propria invaded</td>
<td>T2</td>
<td>T2</td>
<td>L</td>
</tr>
<tr>
<td>210</td>
<td>Stated as T2 with no other information on expansion</td>
<td>T2</td>
<td>T2</td>
<td>L</td>
</tr>
<tr>
<td>300</td>
<td>Localized, NOS, Confined to colon, NOS</td>
<td>^</td>
<td>T1</td>
<td>L</td>
</tr>
<tr>
<td>400</td>
<td>Extension through wall, NOS</td>
<td>T3</td>
<td>T3</td>
<td>L</td>
</tr>
<tr>
<td>410</td>
<td>Stated as T3 with no other information on expansion</td>
<td>T3</td>
<td>T3</td>
<td>L</td>
</tr>
</tbody>
</table>

- Nodes are either Positive or Negative – N0 or N1
- Distant Metastasis are either Positive or Negative – M0 or M1
Staging NET Neoplasms

CS Site-Specific Factors for NET Neoplasms

**Mitotic Count - # mitosis/10HPF**
Note 3: Record mitotic count to the nearest tenth as documented in the pathology report. For example, a mitotic count of 3/10 HPF would be coded = 030.

**Serum CgA (Chromogranin A - Lab Value)**
Note 2: Record to the nearest nanogram/milliliter (ng/ml) the highest CgA lab value documented in the medical record prior to treatment. For example, code a pretreatment CgA of 400 ng/ml = 400

**Urinary 5-HIAA (5-Hydroxyindoleacetic Acid - Lab Value)**
Note 2: Record to the nearest milligram (mg) the highest 5-HIAA lab value documented in the medical record prior to treatment. For example, code pre-treatment 5-HIAA of 550 mg over 24 hours = 550

---

Staging GIST Neoplasms

- Use Specific CS Schema or TNM Chapter
  - GIST Appendix
  - GIST Colon
  - GIST Esophagus
  - GIST Peritoneum
  - GIST Rectum
  - GIST Small Intestine
  - GIST Stomach

- No such thing as Unknown Primary GIST
  - GI Tract, NOS is site if you do not know origin
Staging GIST Neoplasms

Nodes are either Positive or Negative – N0 or N1
Distant Metastasis are either Positive or Negative – M0 or M1
Staging GIST Neoplasms

CS Site-Specific Factors for GIST Neoplasms

Mitotic Count - # mitosis/50HPF

Note 3: Record mitotic count, to the nearest tenth of a mitosis, as documented in the pathology report. For example, a mitotic count of 6/50 HPF, or 6 per 5 square mm = 0.60.

KIT Gene Mutation(s) - also known as CD117

Note 1: This is a special molecular diagnostic test performed on tumor tissue to identify mutations in specific parts (called exons) of the KIT gene. Certain patterns of mutations correlate with the anatomic site and morphology of gastrointestinal stromal tumors (GIST) tumors and can predict response to treatment with agents such as imatinib mesylate (Gleevec) and sunitinib malate (Sutent). Some mutations are associated with acquired resistance to imatinib treatment; do not record secondary or acquired mutations that may have been caused by long-term imatinib treatment.

PDGFRA Gene Mutation - also known as CD140A

Note 1: Some gastrointestinal stromal tumors (GIST) have oncogenic mutations of the platelet-derived growth factor receptor alpha (PDGFRA) gene, located on chromosome 4q. This test is a special molecular diagnostic test performed on tumor tissue to identify PDGFRA mutations. Some GISTs that are negative for KIT mutations are positive for PDGFRA mutation.

<table>
<thead>
<tr>
<th>TNM Stage</th>
<th>TNM</th>
<th>Mitotic Rate</th>
<th>Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>stage IA</td>
<td>T1, T2 N0 M0</td>
<td>low</td>
<td>The tumor is no bigger than 5 cm in diameter. The cancer has not spread to nearby lymph nodes or distant sites. The mitotic rate is low.</td>
</tr>
<tr>
<td>stage IB</td>
<td>T3 N0 M0</td>
<td>low</td>
<td>The tumor is bigger than 5 cm, but not bigger than 10 cm. The cancer has not spread to nearby lymph nodes or distant sites. The mitotic rate is low.</td>
</tr>
<tr>
<td>stage II</td>
<td>T1, T2 N0 M0</td>
<td>high</td>
<td>The tumor is no bigger than 5 cm in diameter. The cancer has not spread to nearby lymph nodes or distant sites. The mitotic rate is high.</td>
</tr>
<tr>
<td>stage IIIB</td>
<td>T4 N0 M0</td>
<td>low</td>
<td>The tumor is bigger than 10 cm. The cancer has not spread to nearby lymph nodes or distant sites. The mitotic rate is low.</td>
</tr>
<tr>
<td>stage IIIA</td>
<td>T3 N0 M0</td>
<td>high</td>
<td>The tumor is bigger than 5 cm, but not bigger than 10 cm. The cancer has not spread to nearby lymph nodes or distant sites. The mitotic rate is high.</td>
</tr>
<tr>
<td>stage IIIB</td>
<td>T4 N0 M0</td>
<td>high</td>
<td>The tumor is bigger than 10 cm. The cancer has not spread to nearby lymph nodes or distant sites. The mitotic rate is high.</td>
</tr>
<tr>
<td>stage IV</td>
<td>any T N1 M0</td>
<td>any rate</td>
<td>The tumor is any size. The cancer has spread to nearby lymph nodes but not to distant sites. The tumor has any mitotic rate.</td>
</tr>
<tr>
<td>stage IV</td>
<td>any T any N M1</td>
<td>any rate</td>
<td>The tumor is any size. The cancer may or may not have spread to nearby lymph nodes. The cancer has spread to distant sites. The tumor has any mitotic rate.</td>
</tr>
</tbody>
</table>
Standard Chemotherapies for GI Tract Tumors such as fluorouracil and oxaliplatin have limited efficacy.

Octreotide (Sandostatin) can slow tumor growth in patients with NET of mid-gut that has metastasized.

Bevacizumab (Avastin) can help limit the growth and spread by stopping angiogenesis, the process of making new blood vessels, which “starves” the tumor.

Alpha Interferon has been used at low doses - toxicity

Source: ASCO.org and American Cancer Society
New Targeted Therapies - NET

- Everolimus (Afinitor) has demonstrated some benefit
- Sunitinib (Sutent) has also demonstrated some benefit
- Both of these drugs are also used to target GIST

<table>
<thead>
<tr>
<th>Targeted Therapy</th>
<th>Agent</th>
<th>Target(s)</th>
<th>Type</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Everolimus</td>
<td>mTOR</td>
<td>mTOR</td>
<td>NM</td>
<td>Gastrointestinal</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>tyrosine kinase 2 (TK2, C-KIT)</td>
<td>mTOR</td>
<td>NET</td>
<td>Patients with PDGFRα or KIT mutations,</td>
</tr>
<tr>
<td>VEGF receptor 2 (VEGFR2)</td>
<td>VEGF</td>
<td>VEGF</td>
<td>NET</td>
<td>Non-randomized</td>
</tr>
</tbody>
</table>

Source: Canadian Cancer Society and US FDA

Various Treatments for NET - Outcomes

Source: www.mja.com.au/Volume 193 Number 1
Other Treatment Options - NET

Tumor Ablation and/or Tumor Embolization

- Radiofrequency ablation (RFA), which uses high-energy radio waves to heat the tumor and destroy cancer cells.
- Ethanol (alcohol) ablation, where concentrated alcohol is injected directly into the tumor to kill cancer cells.
- Microwave thermotherapy, where microwaves transmitted through a probe placed in the tumor are used to heat and destroy the cancer cells.
- Cryosurgery (cryotherapy), which destroys a tumor by freezing it using a thin metal probe. This method sometimes requires general anesthesia (where you are deeply asleep and not able to feel pain).
- Trans-arterial (liver) embolization (TAE), which attempts to block or reduce the blood flow to cancer cells in the liver.

Source: American Cancer Society

NCCN Treatment Guidelines - GIST

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Soft Tissue Sarcoma

Version 2.2014
NCCN.org
NCCN Treatment Guidelines - GIST

Treatment = Surgical Resection and Imatinib (Gleevec)

Other Treatment Options - GIST

- Newer Targeted Agents Similar to Gleevec
- May be Used if Patient Cannot Tolerate Gleevec
- Approved for Use as 2nd and 3rd Line Drugs
  - Sunitinib (Sutent) – after failing Gleevec
  - Regorafenib (Stivarga) – after failing Sutent

Source: American Cancer Society

Tumor Ablation and/or Tumor Embolization

- Radiofrequency ablation (RFA), which uses high-energy radio waves to heat the tumor and destroy cancer cells.
- Ethanol (alcohol) ablation, where concentrated alcohol is injected directly into the tumor to kill cancer cells.
- Microwave thermotherapy, where microwaves transmitted through a probe placed in the tumor are used to heat and destroy the cancer cells.
- Cryosurgery (cryotherapy), which destroys a tumor by freezing it using a thin metal probe. This method sometimes requires general anesthesia (where you are deeply asleep and not able to feel pain).
- Trans-arterial (liver) embolization (TAE), which attempts to block or reduce the blood flow to cancer cells in the liver

Source: American Cancer Society
1. **Go to Training Menu**
2. Select Practical Application Tests
   - Scroll to Bottom of Page
3. Select Type of Practical Application
   - Case Coding – CSV0205
   - Heme 2014 Cases
   - TNM 7th Edition
4. Select Cancer Site – 10+ cases/site
5. Select Case
6. **Start Test**
Ovary 05 Scenario

Abstacted Text
For the purpose of coding this case, assume that the information in the scenario represents the complete information available at the time the case was abstracted.

Social History
Asian female born and raised in Vietnam, moved to area ~2 years ago with husband. Insurance: Medicaid.

Physical Exam
04/12/2014: nr 4 ovarian mass withomental caking. MRI has foul-smelling fluid for last few months. -1 week ago developed severe lower pelvic pain resulting in visit to outside hospital. MRI PTA CT scan 04/09/2014 that showed ovarian mass in upper abdomen, 4.5 x 4.0 x 4.8 cm adjacent to F colon, also a large pelvic mass measuring 3.4 x 1.4 x 1.8 cm, enlarged node in R pelvis, and multiple small pulmonary nodules (cm nodule). Here for further eval. CT Pelvic: Mass in postero cutaneous, cannot distinguish secondary to mass. Ultrasound very difficult to palpate secondary to mass. MRI: Findings show ovarian carcinoma (if not bilateral) vs. simple cyst or basal cell tumor. Plan: FH history of breast cancer, discussed with cardiologist about whether she could undergo surgery now or if neoadjuvant chemo would be best. Cannot start chemo until sure of diagnosis, which will require bi. Then ultimate goal would be to take her to surgery.

Scans
05/21/2014 - CT Abdomen/Pelvis: Interval reduction in size and number of pulmonary nodules. Interval reduction solid component of pelvic mass and size of ovarian mass. Ll ovary normal, rt ovary not separate from mass. Normal liver with normal margins.

Labs
04/08/2014 - CA 125: 1468 UI/mL (0.35 UI/mL, normal)

Operative Reports
04/19/2014 - US: Soft tissue guided core biopsy of ovarian mass: US reveals solid ovarian mass lesion, 5.2 x 3.0 x 4.3 cm in IRLQ.
08/30/2014 - Expl lap, supramesenteric hysterectomy, BSO, appendectomy, lysis of adhesions, argon beam ablation, cystoscopy. Large right pelvic mass, adherent to appendix. Numerous bowel adhesions, mesenterial nodularity. Cystoscopy with no gross residual disease at completion of case. Cystoscopy revealed nontubular mucosa, normal trigone.

Chemo Text
06/26/2014 - Started Carboplatin and Paclitaxel.
06/20/2014 - Started Gemcitabine with Carboplatin. Chemo changed due to severe nausea, diarrhea, altered liver function after 1st cycle chemo.

Practice Cases

08/20/2014 - Path Report #2

Clinical Diagnosis/History:
History of advanced Mullerian adenocarcinoma, status post neoadjuvant chemo with excellent response (decreased disease on CT, exam CA 125) - 180.

Final Diagnosis:
A. C, E and H: Right tube and ovary and appendice, reaction, uterus, left tube and ovaries, reaction; Pelvic lymph node, excision and multiple biopsies as designated:
1. Right ovary replaced by cystic mass with extensive necrosis and characteristics suggestive of treated neoplasm. No definitive fallopian tube identified in specimen. Appendix uninvolved by neoplasm.
2. Mesothelial like cells and foreign body giant cells on uterus serosa and myometrium and in multiple biopsies (small bowel adhesions, implants and diaphragm) consistent with treated neoplasm; no viable neoplasm identified.
3. One pelvic lymph node with foamy macrophages consistent with treated neoplasm; no viable neoplasm identified.
4. Inflamed endometrium, left fallopian tube with paratubal cysts, and inactive left ovary with no neoplasm identified.
D. Small bowel nodule, biopsy: Fibromuscular tissue with pseudocystic but no definitive neoplasm identified.
G2. Diaphragmatic adhesions, biopsy: Organizing hematoma.
H. Omentum, resection: Omental tissue with no neoplasm identified.

Gross Description:
Specimen A: Received in formalin labeled "right tube and ovary, and appendix" is a 601 g, 24.0 x 13.0 x 10.0 cm irregular multinodular mass with attached 9.0 x 5.5 cm tubular structure. The specimen is covered in a gelatinous tan pink to focally bright red mass. The largest mass is predominantly cystic and consists of a large amount of yellow liquified material and some salmon pink liquified material. One of the nodules is filled with slightly more solid yellow to tan partially liquified material. A small dilator, measuring approximately 3.0 cm x 0.2 cm in diameter is identified and thought represent a fallopian tube. Representative sections are submitted as follows.
A1. Tubular structure (previously)
A2. Entire fallopian tube
A3. Main cystic mass
A4-A7. Additional cystic mass

Specimen B: Received fresh in a bag labeled "uterus, left tube and ovary" is a 50 g uterus with left tube and ovary attached. The uterine measures 6.0 cm x 5.0 cm laterally x 2.3 cm AP. The tube is 3.5 x 0.5 cm. The ovary is 2.5 x 1.5 x 1.0 cm and it has multiple semilunar cysts ranging in size from 0.5 cm to 1.0 cm. This is a supramesenteric hysterectomy specimen. The
Practice Cases

Correct

Correct [1.00/1.00]

Data Item: Laterality
Response: 1
Correct Answer: 1

Rationale:
The 04/12/2014 physical exam note documented the patient had a right ovarian mass. The 05/21/2014 CT scan noted the left ovary was normal. The resection pathology report, though negative for residual malignancy, showed the right ovary was replaced by a cystic mass, while the left ovary showed no definitive neoplasm. The clinical and pathological information indicates the carcinoma involved the right ovary only. Per the SEER Manual, every is a paired site. Apply code 1 when the right side of a paired site is involved.

(2014 SEER Manual, Laterality.)

Error

Incorrect [0.00/3.00]

Data Item: Histology
Response: 0140
Correct Answer: 0110

Rationale:
The MAPT Rules (general rules) state to code the histology from a metastatic site when there is no pathology/cytology specimen from the primary site. The pathology report from the omentum mass biopsy was positive for carcinoma, NOS. The clinical diagnoses on the cytoreductive surgery pathology report was malignant adenocarcinoma. However, no residual malignancy was identified per the cytoreductive surgery pathology report. The patient only had histologic confirmation of carcinoma, NOS from a metastatic site (omentum). A pathologic diagnosis has priority over a clinical diagnosis. Code the histology as NOS (carcinoma, NOS).

(2007 Multiple Primary and Histology Coding Rules)

Additional Resources

- CDC Information about NET and GIST Neoplasms
- American Cancer Society and Canadian Cancer Society
- NCI Physician Data Query for Healthcare Professionals
- WHO Classification of Tumors of Endocrine Origin, WHO, 2004
- Multiple Primary and Histology Coding Rules, SEER 2007
- Collaborative Stage Data Collection System, AJCC, 2012
- NCCN Evidence Based Treatment Guidelines, NCCN, 2015
- American Society of Clinical Oncology, ASCO, 2015
- NAACCR Cancer Registry Webinar Series
- SEER Training for Cancer Registry Professionals
- SEER Educate for Practice Cases and Other Training
- H. Lee Moffitt Cancer Center, Jonathan Strosberg, MD
Questions
NCRA CEU # 2014-118