NET / GIST / MEN

2014/2015 FCDS Educational Webcast Series

October 16, 2014

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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 7thed, 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.

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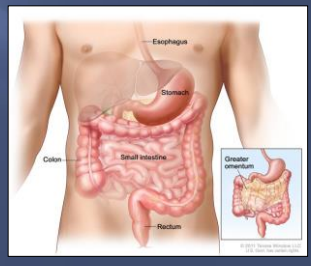
Presentation Outline

- 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



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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.

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Endocrine System Link to Nervous System

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.

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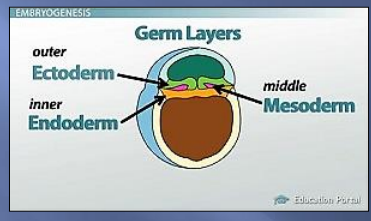
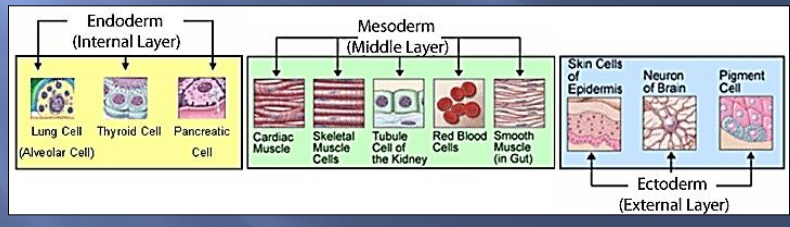
Embryonic Development – Germ Layers





Source: www.biologyjunction.com and education-portal.com

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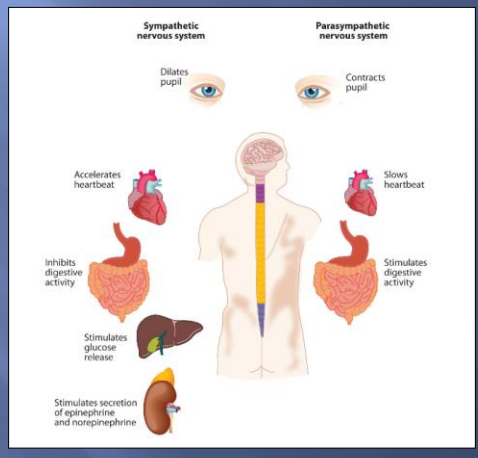
Autonomic Nervous System



Source: images.flatworldknowledge.com

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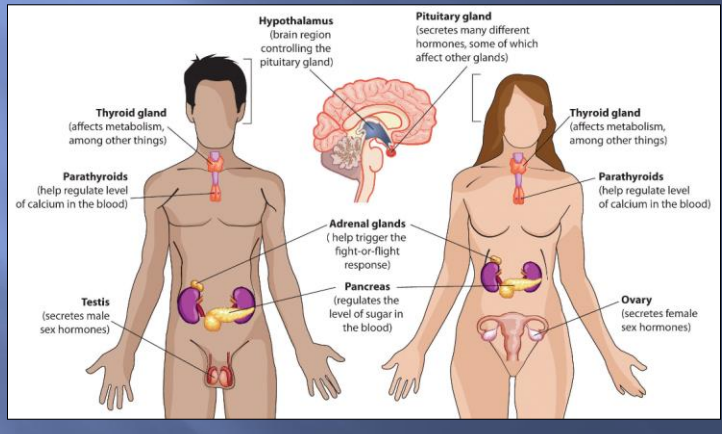
The Endocrine System - A&P



Source: images.flatworldknowledge.com

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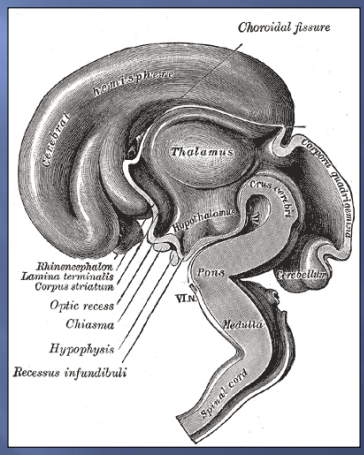
The Hypothalamus - A&P



Source: Gray654 – Gray's Anatomy (public domain)

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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

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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

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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 tiesues 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.

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Hormone Regulation – Form & Function

SERUM HORMONE EVALUATION POTENTIALLY INDICATED IN THE WORKUP OF NEUROENDOCRINE TUMORS[1]

HORMONE-RELATED STUDIES (blood markers)

- Carcinoid tumors
  - 5-HIAA (24-hour urine)
  - Chromogranin A (category 3)
- PanNET
  - Chromogranin A (category 3)
- Gastrinoma
  - Gastrin
- 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)[2]
- Pituitary
  - Growth hormone/IGF-1
  - Prolactin
  - LH/FSH
  - TSH
  - Alpha subunits
  - ACTH
- Ectopic hormones
  - ACTH
  - GRH
  - GHRH

Source: www.nccn.org/neuroendocrine.pdf

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Hormone Regulation – Form & Function

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

Speel EJM et al. Am J Pathol. 1999;155:1787–1794 and Rindi G, et al. Ann NY Acad Sci. 2004;1014:1-12

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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.

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What is a "Functional" Tumor?

- 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.

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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)

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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.

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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.

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The GI Tract – GIST

Source: www.executivetravel.com

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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.

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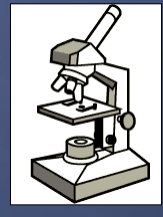
WHO Classification – GIST

- 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)

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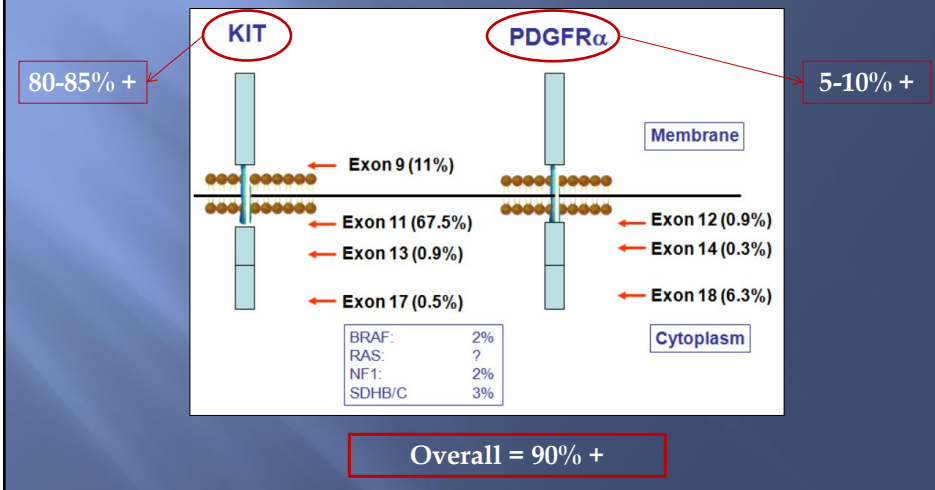
WHO Classification – GIST



Overall = 90% +

Source: Discovery Medicine.com/Jean-Yves-Blay

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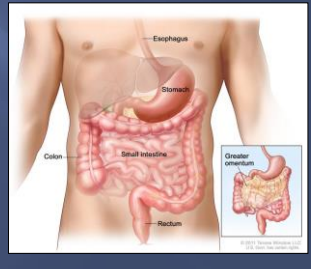
WHO Classification – GIST

- 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



Source: www.cancer.gov/cancertopics/pdq/treatment/gist

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WHO Classification – GIST

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

Mitotic Index, hpf	Size, cm	Site and Risk of Progressive Disease (%)			
		Gastric	Duodenum	Jejunum/Ileum	Rectum
≤5 per 50	≤2	None (0)	None (0)	None (0)	None (0)
	>2 ≤5	Very low (1.9)	Low (4.3)	Low (8.3)	Low (8.5)
	>5 ≤10	Low (3.6)	Moderate (24)	(Insufficient data)	(Insufficient data)
	>10	Moderate (10)	High (52)	High (34)	High (57)
>5 per 50	≤2	None	High[b]	(Insufficient data)	High (54)
	>2 ≤5	Moderate (16)	High (73)	High (50)	High (52)
	>5 ≤10	High (55)	High (85)	(Insufficient data)	(Insufficient data)
	>10	High (86)	High (90)	High (86)	High (7)

Source: www.cancer.gov/cancertopics/pdq/treatment/gist

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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

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WHO Classification – NET

- 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

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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 mm^2. Ten HPF is equivalent to 2 mm^2 on many microscopes, although the field size may vary slightly.[4]
- 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 2000 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.[10]
- 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.[11]

Table 1

Grade	Gastroenteropancreatic (GEP) NETs	Lung and Thymus	Differentiation
Low Grade (G1)	<2 mitoses/10 HPF AND/OR <3% Ki-67 index	<2 mitoses/10 HPF AND no necrosis	Well-differentiated NET
Intermediate Grade (G2)	2-20 mitoses/10 HPF AND/OR 3-20% Ki-67 index	2-10 mitoses/10 HPF AND/OR foci of necrosis	Well-differentiated NET
High Grade (G3)	>20 mitoses/10 HPF AND/OR >20% Ki-67 index	>10 mitoses/10 HPF	Poorly differentiated neuroendocrine carcinoma

Adapted from Bosman FT, Carneiro F, Hruban RH, Theise ND. World Health Organization Classification of Tumours of the Digestive System. IARC, Lyon, 2010; and Travis WD, Brambilla E, Muller-Hermelink HK, Harris CC. World Health Organization Classification of Tumours of the Lung, Pleura, Thymus and Heart. Lyon: IARC; 2004.

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 NET as a "poorly differentiated NEC." In these cases, the tumor should be reported as a well-differentiated NET (so-called "atypical carcinoid" terminology in lung and thymus) with the specific mitotic rate and Ki-67 proliferation index included in the report as additional information (See NE-A 3 of 4).

Source: www.nccn.org/neuroendocrine.pdf

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Mitotic Rate (Index) and Grade – GIST

Grade	Mitotic rate	Number of mitoses per 50 high-power fields (HPF)
low	low	less than 5
high	high	more than 5

DOES MITOTIC RATE (INDEX) EFFECT STAGE?

- YES -

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Mitotic Rate and TNM Stage – GIST

TNM Stage	TNM			Mitotic Rate	Explanation
stage IA	T1,T2	N0	M0	low	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.
stage IB	T3	N0	M0	low	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.
stage II	T1, T2	N0	M0	high	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.
	T4	N0	M0	low	The tumour is bigger than 10 cm. The cancer has not spread to nearby lymph nodes or distant sites. The mitotic rate is low.
stage IIIA	T3	N0	M0	high	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.
stage IIIB	T4	N0	M0	high	The tumour is bigger than 10 cm. The cancer has not spread to nearby lymph nodes or distant sites. The mitotic rate is high.
stage IV	any T	N1	M0	any rate	The tumour is any size. The cancer has spread to nearby lymph nodes but not to distant sites. The tumour has any mitotic rate.
	any T	any N	M1	any rate	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.

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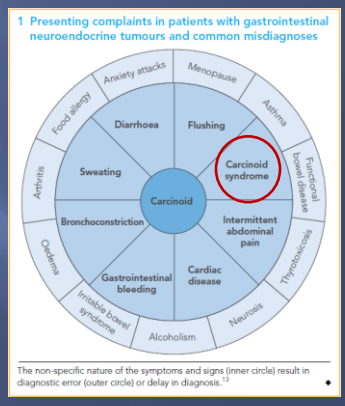
Signs and Symptoms

- 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

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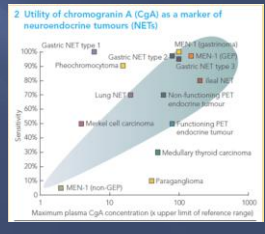
Tumor Markers - NET

- 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



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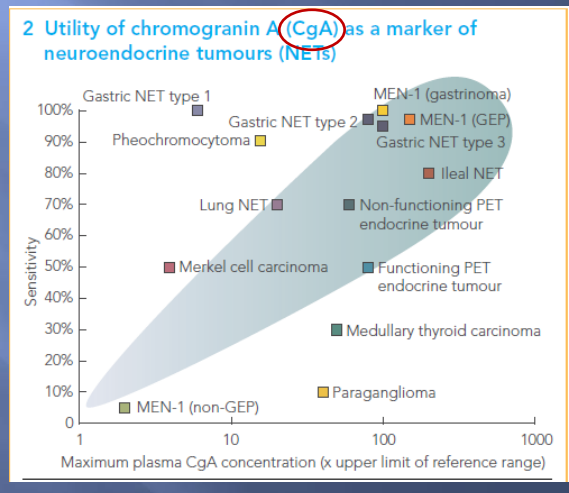
Tumor Markers - NET



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

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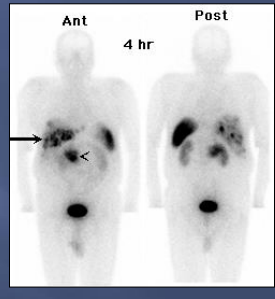
Somatostatin Receptors and Octreotide

	In vivo	
GH-producing pituitary tumour	7/10	70%
TSH-producing pituitary tumour	2/2	100%
Non-functioning pituitary tumour	12/16	75%
Gastrinoma	12/12	100%
Insulinoma	14/23	61%
Glucagonoma	3/3	100%
Unclassified APUDoma	16/18	89%
Paraganglioma	33/33	100%
Medullary thyroid carcinoma	20/28	71%
Neuroblastoma	8/9	89%
Pheochromocytoma	12/14	86%
Carcinoid	69/72	96%
Small cell lung cancer	34/34	100%



Source: www.med.harvard.edu

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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

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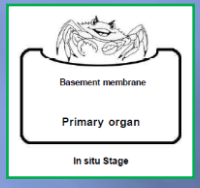
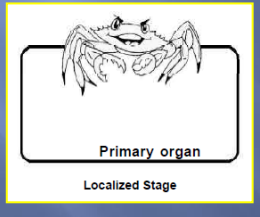
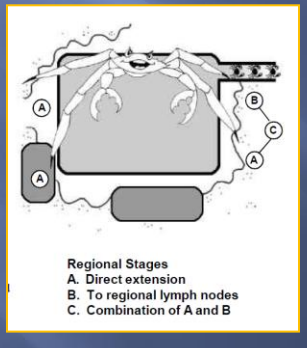
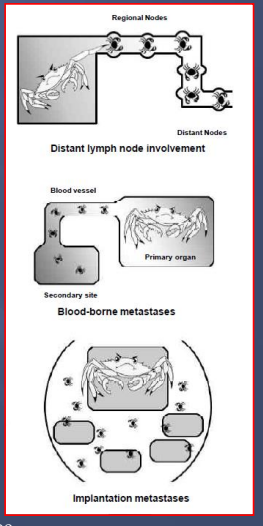
SEER Summary Stage





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





Source: SEER Summary Staging Manual 2000

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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

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Staging NET Neoplasms

- 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.

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Staging NET Neoplasms

170	Stated as T1a with no other information on extension	^	T1	L	L
180	Stated as T1b with no other information on extension	^	T1	L	L
190	Stated as T1 [NOS] with no other information on extension	^	T1	L	L
200	Muscularis propria invaded	T2	T2	L	L
210	Stated as T2 with no other information on extension	T2	T2	L	L
300	Localized, NOS Confined to colon, NOS	^	T1	L	L
400	Extension through wall, NOS Through muscularis propria or muscularis, NOS Non-peritonealized pericolic tissues invaded Perimuscular tissue invaded Subserosal tissue/(sub)serosal fat invaded Transmural, NOS	T3	T3	L	L
410	Stated as T3 with no other information on extension	T3	T3	L	L

✓ Nodes are either Positive or Negative – N0 or N1
✓ Distant Metastasis are either Positive or Negative – M0 or M1

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Staging NET Neoplasms

Staging

American Joint Committee on Cancer (AJCC)
TNM Staging System for Neuroendocrine Tumors (gastric, small bowel, colonic, rectal, and ampulla of Vater carcinoid tumors [well-differentiated neuroendocrine tumors and well-differentiated neuroendocrine carcinomas]) (7th ed., 2010)

Colon or Rectum
TNM

Primary Tumor (T)

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor invades lamina propria or submucosa and size 2 cm or less
T1a	Tumor size less than 1 cm in greatest dimension
T1b	Tumor size 1–2 cm in greatest dimension
T2	Tumor invades muscularis propria or size more than 2 cm with invasion of lamina propria or submucosa
T3	Tumor invades through the muscularis propria into the subserosa, or into non-peritonealized pericolic or perirectal tissues
T4	Tumor invades peritoneum or other organs For any T, add (m) for multiple tumors

Regional Lymph Nodes (N)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis

Distant Metastases (M)

M0	No distant metastases
M1	Distant metastasis

ANATOMIC STAGE/PROGNOSTIC GROUPS

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage IIA	T2	N0	M0
Stage IIB	T3	N0	M0
Stage IIIA	T4	N0	M0
Stage IIIB	Any T	N1	M0
Stage IV	Any T	Any N	M1

✓ Nodes are either Positive or Negative – N0 or N1
✓ Distant Metastasis are either Positive or Negative – M0 or M1

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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-Hydroxyinidoleacetic 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

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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

COLLABORATIVE STAGE DATA COLLECTION SYSTEM

AJCC American Joint Committee on Cancer

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

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Staging GIST Neoplasms

165	Tumor invades through submucosa and muscularis mucosae to involve mucosa	^	NA	L	L
200	OBSOLETE DATA RETAINED AND REVIEWED V0203 See codes 155 and 165 Invades into but not through muscularis propria	^	NA	L	L
300	Implants inside stomach Localized, NOS	^	NA	L	L
340	Stated as T1 with no other information on extension	^	NA	L	L
350	OBSOLETE DATA RETAINED V0200 Linitis plastica and no other information regarding extension is available	ERROR	NA	RE	L
390	Stated as T2 with no other information on extension	^	NA	L	L
395	Stated as T3 with no other information on extension	^	NA	L	L
398	Stated as T4 with no other information on extension	^	NA	L	L
400	Invasion through muscularis propria or muscularis, NOS Extension through wall, NOS Perimuscular tissue invaded Subserosal tissue/(sub)serosal fat invaded	^	NA	L	L

- ✓ Nodes are either Positive or Negative – N0 or N1
- ✓ Distant Metastasis are either Positive or Negative – M0 or M1

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Staging GIST Neoplasms

Table 1: Gastric GISTs: Proposed Guidelines for Assessing the Malignant Potential[1,2]

Tumor Size	Mitotic Rate	Predicted Biologic Behavior
≤2 cm	≤5 mitoses/50 HPFs	Benign, metastasis rate or tumor-related mortality: 0
>2cm ≤10 cm	≤5 mitoses/50 HPFs	Very low malignant potential, metastasis rate or tumor-related mortality: <4%
≤5 cm	>5 mitoses/50 HPFs	Low to moderate malignant potential, metastasis rate or tumor-related mortality: 12% to 15%
>10 cm	≤5 mitoses/50 HPFs	
>5 cm	>5 mitoses/50 HPFs	High malignant potential, metastasis rate or tumor-related mortality: 49% to 86%
GISTs: Gastrointestinal stromal tumors; HPFs: High-power fields		

- ✓ Nodes are either Positive or Negative – N0 or N1
- ✓ Distant Metastasis are either Positive or Negative – M0 or M1

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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 = 060.

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.

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Tumor Size, Mitotic Rate and Stage – GIST

TNM Stage	TNM			Mitotic Rate	Explanation
stage IA	T1,T2	N0	M0	low	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.
stage IB	T3	N0	M0	low	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.
stage II	T1, T2	N0	M0	high	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.
	T4	N0	M0	low	The tumour is bigger than 10 cm. The cancer has not spread to nearby lymph nodes or distant sites. The mitotic rate is low.
stage IIIA	T3	N0	M0	high	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.
stage IIIB	T4	N0	M0	high	The tumour is bigger than 10 cm. The cancer has not spread to nearby lymph nodes or distant sites. The mitotic rate is high.
stage IV	any T	N1	M0	any rate	The tumour is any size. The cancer has spread to nearby lymph nodes but not to distant sites. The tumour has any mitotic rate.
	any T	any N	M1	any rate	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.

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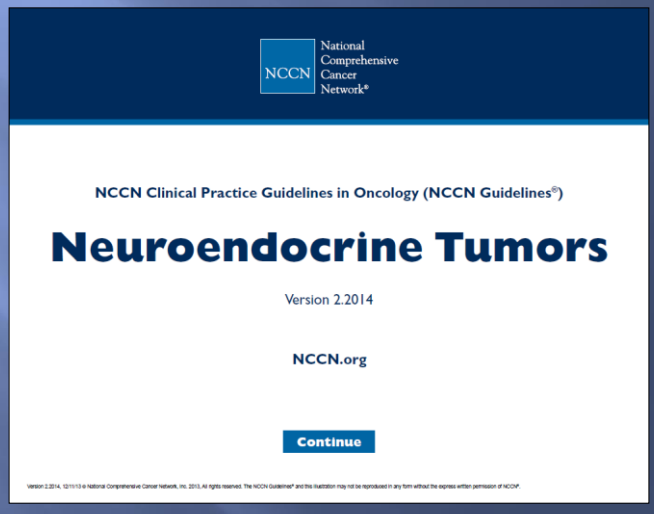
NCCN Treatment Guidelines - NET



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NCCN Treatment Guidelines - NET

CLINICAL PRESENTATIONS AND DIAGNOSIS[a]

Carcinoid tumors[b]
Clinical presentations:
- Jejunal, ileal, colon (See CARC-1)
- Duodenal (See CARC-1)
- Appendix (See CARC-2)
- Rectal (See CARC-3)
- Gastric (See CARC-4)
- Bronchopulmonary, thymus (See CARC-5)
- Atypical lung carcinoid
- Locoregional unresectable disease and/or distant metastases (See CARC-6)

Neuroendocrine tumors of the pancreas[b]
Clinical presentations:
- Nonfunctioning pancreatic tumors (See PanNET-1)
- Gastrinoma (See PanNET-2)
- Insulinoma (See PanNET-3)
- Glucagonoma (See PanNET-4)
- VIPoma (See PanNET-5)
- Recurrent disease (See PanNET-6)
- Locoregional unresectable disease and/or distant metastases (See PanNET-7)

Neuroendocrine tumors of unknown primary (See NUP-1)[b]

Adrenal gland tumors (See AGT-1)[c]

Pheochromocytoma/paraganglioma (See PHEO-1)

Poorly differentiated (high grade) neuroendocrine tumors/ Large or small cell carcinoma other than lung (See HGNET-1)

Multiple endocrine neoplasia, type 1 (See MEN1-1)
- Parathyroid
- Pancreatic neuroendocrine tumors (PanNET)
- Pituitary tumor

Multiple endocrine neoplasia, type 2 (See MEN2-1)
- Medullary thyroid carcinoma (Also see NCCN Guidelines for Thyroid Carcinoma)
- Parathyroid
- Pheochromocytoma

Merkel cell carcinoma (See NCCN Guidelines for Merkel Cell Carcinoma)

Source: NCCN Guidelines for Neuroendocrine Tumors -Version 2.2014

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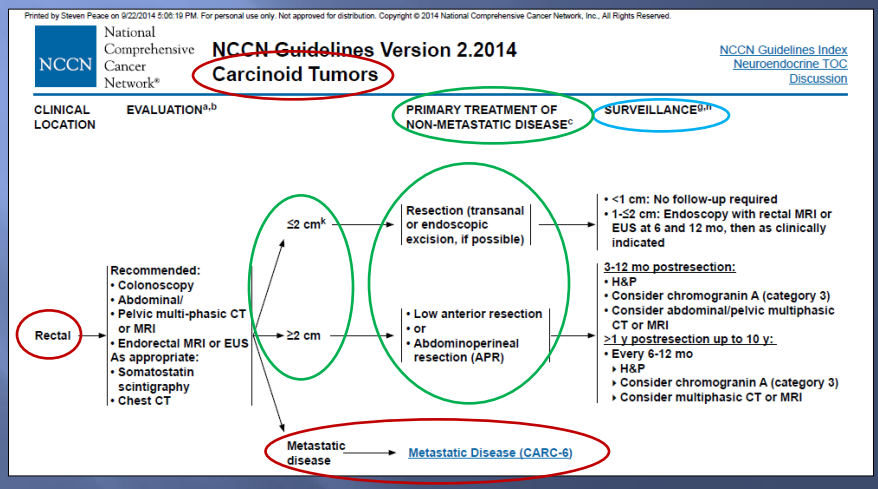
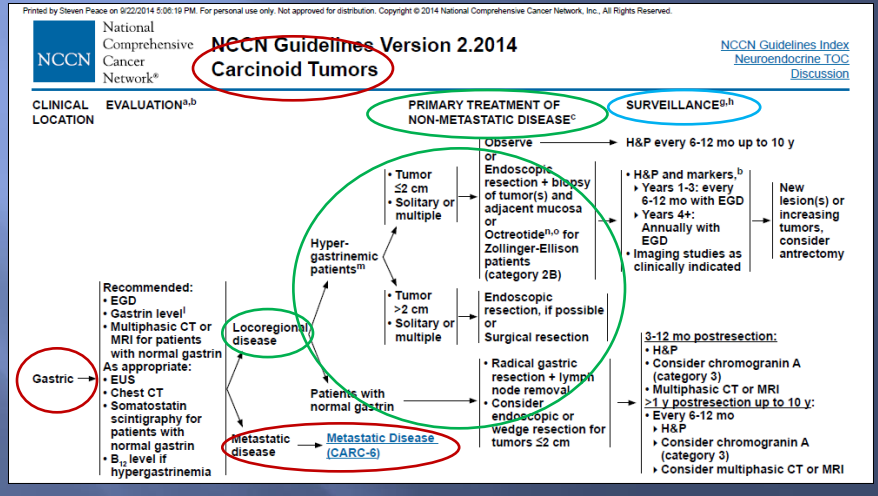
NCCN Treatment Guidelines - NET



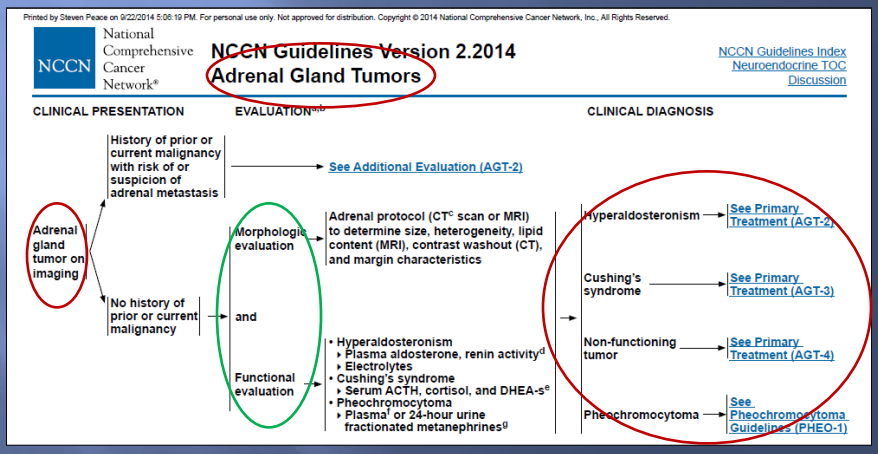
Source: NCCN Guidelines for Neuroendocrine Tumors -Version 2.2014

NCCN Treatment Guidelines - NET



Source: NCCN Guidelines for Neuroendocrine Tumors -Version 2.2014

NCCN Treatment Guidelines - NET



Source: NCCN Guidelines for Neuroendocrine Tumors -Version 2.2014

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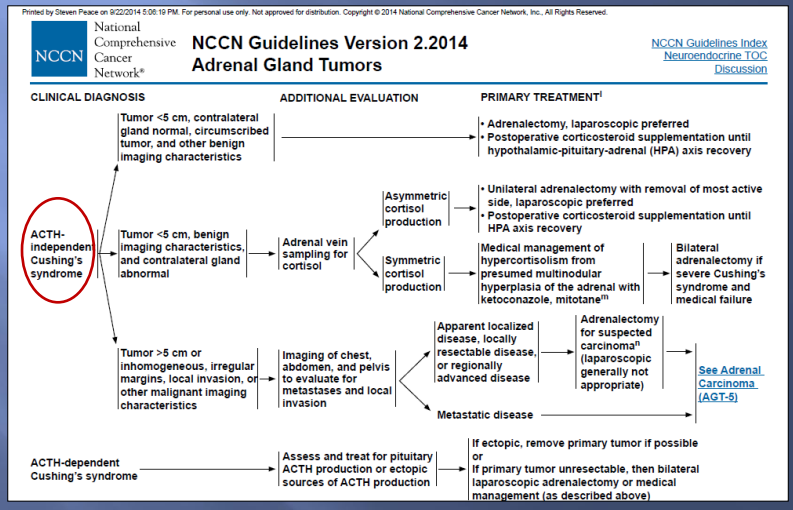
NCCN Treatment Guidelines - NET



Source: NCCN Guidelines for Neuroendocrine Tumors -Version 2.2014

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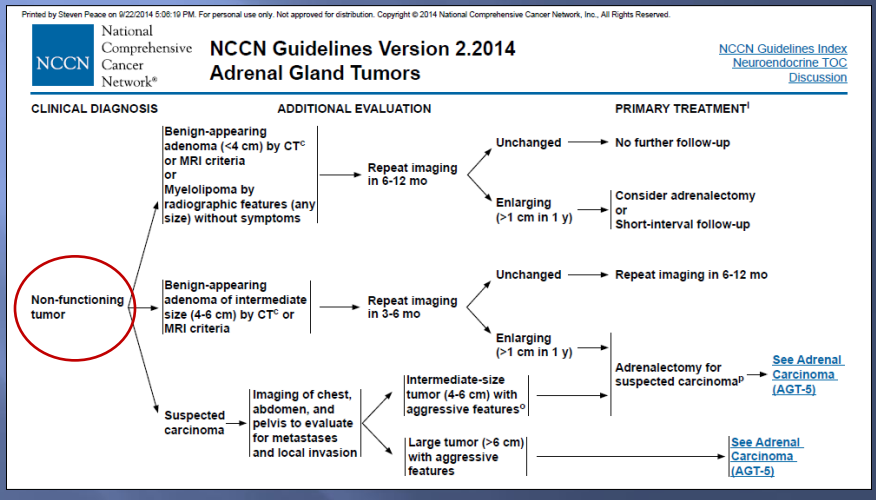
NCCN Treatment Guidelines - NET



Source: NCCN Guidelines for Neuroendocrine Tumors -Version 2.2014

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Targeted Therapies - NET

- 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

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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 2

Ongoing Random Assignment Phase III Study With Targeted Agents in Neuroendocrine Tumors

Agent(s)	Target(s)	N	Tumor Type	Comments
Everolimus vs placebo (RADIANT 2)	mTOR	390	Carcinoid	Patients with PD at entry
Everolimus vs placebo (RADIANT 3)	mTOR	392	PNET	Patients with PD at entry
Octreotide + bevacizumab vs octreotide + interferon alfa-2b	VEGF	283	Carcinoid	Poor prognosis
Sunitinib vs placebo	VEGF, PDGFR, c-Kit, RET, FLT3	340	PNET	Patients with PD at entry

mTOR = mammalian target of rapamycin; NR = not reported; ORR = objective response rate; PD = progressive disease; PDGFR = platelet-derived growth factor receptor; PFS = progression-free survival; PNET = pancreatic neuroendocrine tumors; TTP = time to tumor progression; VEGF = vascular endothelial growth factor.

Source: Canadian Cancer Society and US FDA

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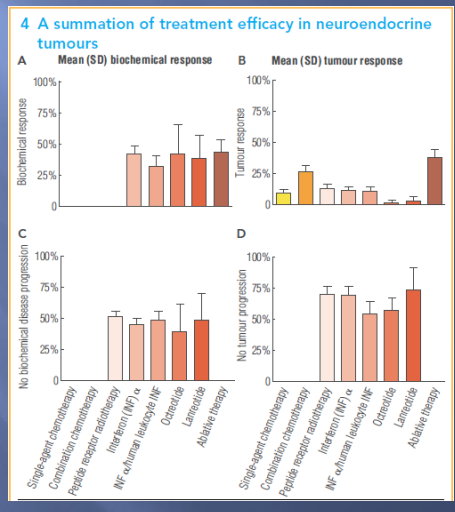
Various Treatments for NET - Outcomes



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

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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

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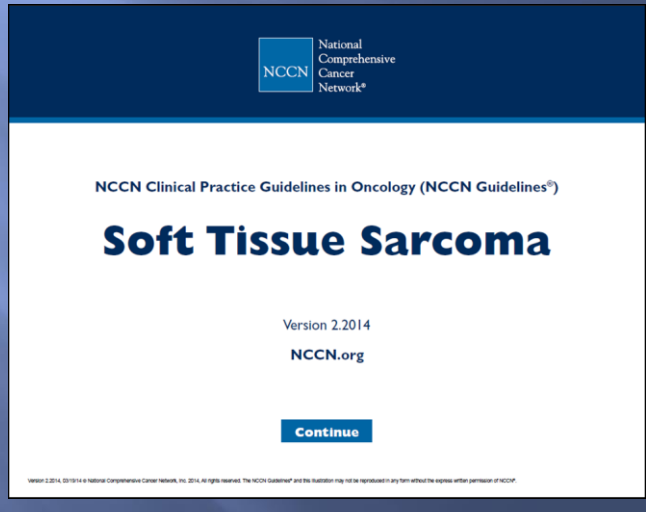
NCCN Treatment Guidelines - GIST



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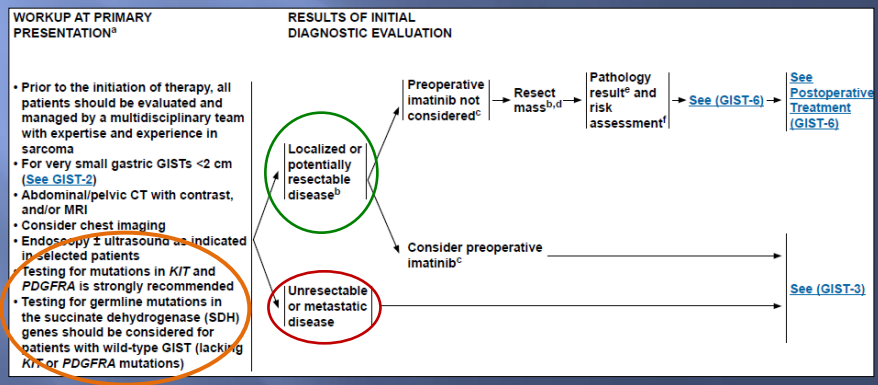
NCCN Treatment Guidelines - GIST

Treatment = Surgical Resection and Imatinib (Gleevec)



Source: NCCN Guidelines for Sarcoma/GIST - Version 2.2014

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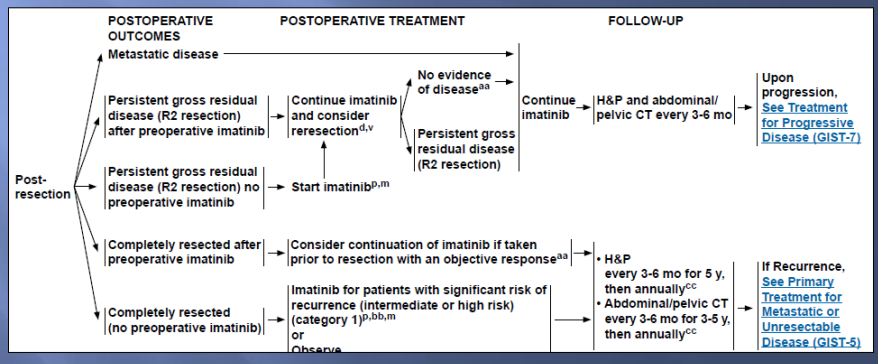
NCCN Treatment Guidelines - GIST

Treatment = Surgical Resection and Imatinib (Gleevec)



Source: NCCN Guidelines for Sarcoma/GIST - Version 2.2014

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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

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Other Treatment Options - GIST

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

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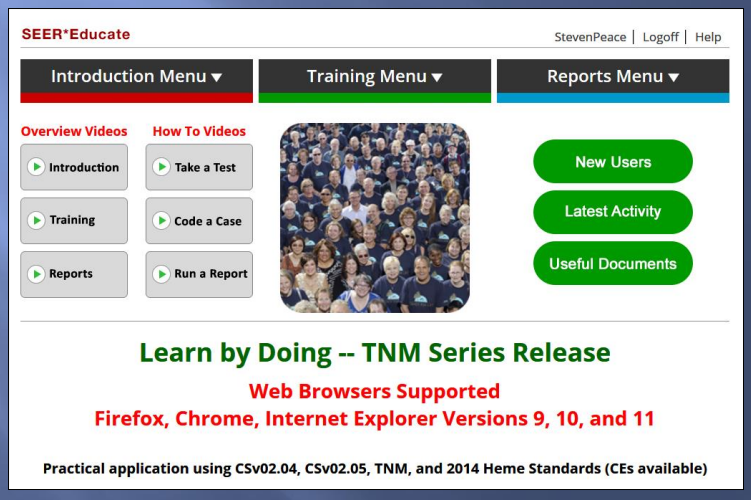
Practice Cases

https://educate.fhcrc.org/Index.aspx



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Practice Cases

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

practice review

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Practice Cases

Test Information and Instruction — Ovary 05 New Window

Name:	Ovary 05
Series:	Practical Application > Case Coding - CSv0205 > Ovary
Description:	A case scenario is a summary of the patient's cancer story as documented in the available medical record. The scenario is used by the cancer registrar to support codes selected for tumor, staging and treatment related data items. While we believe we have recorded the best answer for all fields, we recognize that others might believe a different answer is a better choice. We will track the responses for all data items. For data items with less than 85% agreement with the preferred answer, the CTR panel will review the case scenario again. When necessary, the panel will also contact the appropriate standard setter and request that existing documentation be clarified to improve coding consistency. The case scenarios used in the CSv02.05 coding exercises were created from de-identified abstracts. 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. In addition to the abstracted text, the scenarios include the full text of de-identified and modified pathology reports.
Resources:	The coding form you are about to use has look-ups that contain descriptions for every data item. The collaborative stage data items display the codes and notes for CSv02.05. The cases have been coded using SEER guidelines; therefore, you may want to have the SEER Multiple Primary and Histology Coding Rules, SEER Program Coding and Staging Manual for 2014 and SEER Summary Staging Manual 2000 available. 2014 SEER manual http://www.seer.cancer.gov/tools/codingmanuals/ 2007 Multiple Primary and Histology Coding Rules http://seer.cancer.gov/tools/mphrules/2007_mphrules_manual_08242012.pdf 2000 SEER Summary Staging Manual http://seer.cancer.gov/tools/ssm/SSSM2000-122012.pdf
Instructions:	**PTA is a standard abbreviation for prior to admission. This abbreviation is used throughout the scenarios**

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Practice Cases

Open Case

Test Information and Instruction — Ovary 05 New Window

Coding Form

Click here to open the case scenario required for the test in a new window.

Instructions

Patient Demographics

Sex | Race 1 | Race 2 | Race 3 | Race 4 | Race 5 | Hispanic | Birth State | Birth Country | Vital Status | Last Contact Date

Diagnosis

Diagnosis Date | Sequence Number | Primary Site | Laterality | Histology | Behavior | Grade | Diagnostic Confirmation | Marital Status at DX | Primary Payer at DX

Staging

CS Size | CS Extension | CS Size/Ext Eval | CS LN | CS LN Eval | Reg LN Pos | Reg LN Exam | CS Mets | CS Mets Eval | CS Mets - Bone | CS Mets - Brain | CS Mets - Liver | CS Mets - Lung

Site Specific Factors & Summary Staging

Note: will display after site and histology are entered

SS 2000

Summary Treatment (First Course of Therapy)

Surgery

Reason No Surgery | Surgery Date | Surgery of Primary Site | Scope Reg LN Surgery | Surgery Other Reg Distant

Radiation

Radiation | Radiation Date | Radiation/Surgery Sequence

Systemic

Systemic/Surgery Sequence | Rx Date--Systemic

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Practice Cases

Ovary 05 Scenario

Print

Abstracted 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 rasied in Vietnam, moved to area ~ 2 years ago with husband. Insurance: Medicaid.

Physical Exam

04/12/2014 - cc: Rt ovarian mass with omental caking. HPI: Has had lower abd pain for last few months, ~1 week ago developed severe lower pelvic pain resulting in visit to outside hospital ER. Had PTA CT scan 04/06/2014 that showed omental mass in upper abd, 4.9 x 4.0 x 4.8 cm adjacent to T-colon, also a large pelvic mass measuring 24 x 14 x 18 cm, enlarged node in Rt pelvis, and multiple small pulmonary nodules c/w mets. Here for further eval. PE: Pelvis: Mass palp in posterior cul-de-sac. Cervix difficult to visualize secondary to mass. Uterus/adnexa difficult to palpate secondary to mass. IMP: Findings c/w ovarian carcinoma w/omental and pelvic sidewall mets and pulmonary mets. Plan: Pt has extensive cardiac history, 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 bx. Then ultimate goal would be to take her to surgery.

Scans

05/21/2014 - CT Abd/Pelvis: Interval reduction in size and number of pulmonlary nodules. Interval reduction solid component of pelvic mass and size of omental nodules. Lt ovary normal, rt ovary not separate from mass. Cirrhotic liver w/nodular margins.

Labs

04/08/2014 - CA-125: 1408 U/mL (0-35 U/mL normal)

Operative Reports

04/19/2014 - U/S Soft tissue guided core biopsy of omental mass: U/S reveals solid omental mass lesion, 5.2 x 3.0 x 4.3 cm in RUQ.

08/20/2014 - Expl lap, supracervical hysterectomy, BSO, appendectomy, lysis of adhesions, argon beam ablation, cystoscopy: Large rt pelvic mass, adherent to appendix. Numerous bowel adhesions, omental nodularity. Cytoreduction with no gross residual disease at completion of case. Cystoscopy revealed nml bladder mucosa, normal trigone.

Chemo Text

04/26/2014 - 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.

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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) - 183.0.

Final Diagnosis:

A -C, E and F) Right tube and ovary and appendix, resection; Uterus, left tube and ovaries, resection; 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. Microcalcifications and foreign body type giant cells on uterine 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. Inactive endometrium, left fallopian tube with paratubal cysts, and inactive left ovary with no neoplasm identified.

D) Small bowel nodule, biopsy: Fibromuscular tissue with mesothelial cyst and no definitive neoplasm identified.

G) Diaphragmatic adhesion, biopsy: Organizing hematoma.

H) Omentum, resection: Omental tissue with no neoplasm identified.

Gross Description:

Specimen A: Received in a container of 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 0.5 cm tubular structure. The specimen is covered in a glistening tan-pink to focally bright red serosa. The largest mass is predominantly cystic and consists of a large amount of yellow liquefied material and some salmon-pink liquefied material. One of the nodules is filled with slightly more-solid yellow to tan partially liquefied material. A small sliver, 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 (putative appendix)
A2 - entire putative 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 uterus measures 6.0 cm Sl x 5.0 cm laterally x 2.5 cm AP. The tube is 3.0 x 0.5 cm. The ovary is 3.0 x 1.5 x 1.0 cm and it has multiple semilucent cysts ranging in size from 0.5 cm to 1.0 cm. This is a supracervical hysterectomy specimen. The

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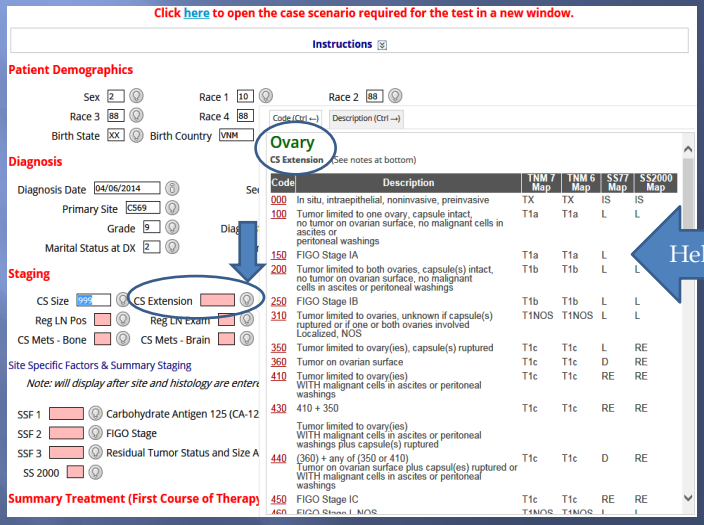
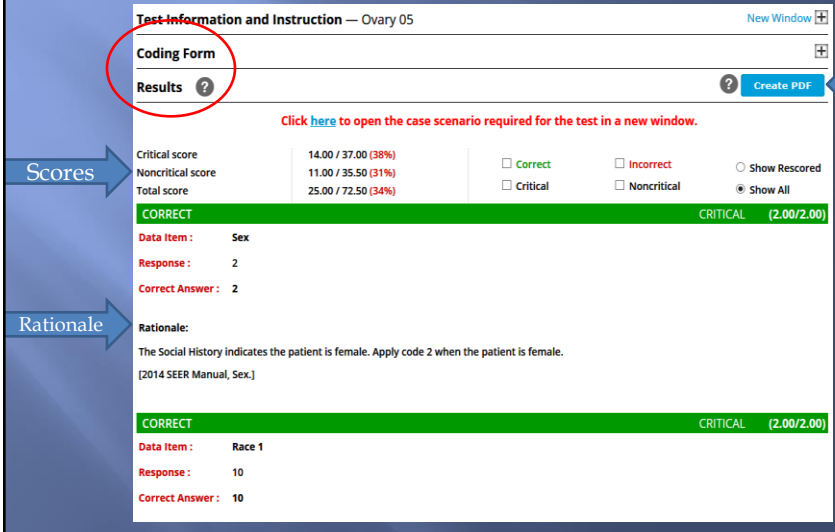
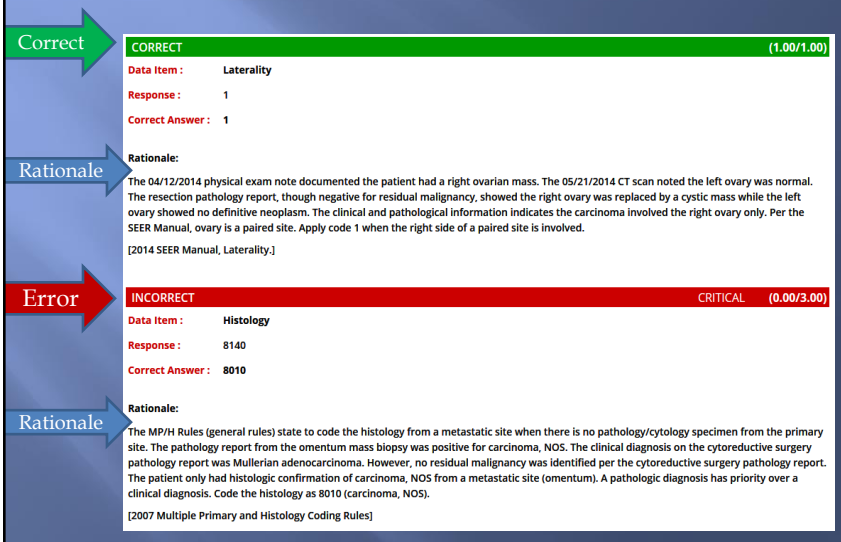
Practice Cases



Practice Cases



Practice Cases



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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

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Questions

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