Small Bowel Carcinoid

Ana M. Grau, MD, FACS
Associate Professor
Division of Surgical Oncology and Endocrine Surgery
Small Bowel Carcinoid

- Introduction, History, Epidemiology
- Macroscopic and Microscopic Appearance
- Clinical Presentation and Diagnosis
- Treatment of Primary
- Treatment of Advanced/Metastatic
- F/U and Prognosis
Carcinoids are neuroendocrine neoplasms that most frequently occur in the GI tract. They originate from endocrine cells in the submucosa. Langhans in 1867 and Lubarsch in 1888 described unusual tumors in the small bowel. In 1907 Oberndorfer referred to them as *Karzinoide* or carcinoma-like, because of their relative indolent nature compared with carcinomas.
In 1897, Nikolai Kulchitsky described the ‘unique’ cells of the intestinal epithelium.

Eponymously referred to as Kulchitsky cells.

Currently referred to as enterochromaffin (EC) cells.
1907 Oberndorfer coins the term “karzinoide” to describe SB submucosal tumors

1914 Gosset and Masson suggest that carcinoids may arise from EC cells

1978 Use of somatostatin to control carcinoid flushing

1982 Synthesis of somatostatin analogues

1985 First successful use of somatostatin analogues in carcinoid disease

1989 Somatostatin scintigraphy

1992 Peptide receptor radiotherapy trials begin

1998 Depot SST analogues

1992 Peptide receptor radiotherapy trials begin

2000 WHO classification Gastrointestinal Neuroendocrine Tumors

Timeline/From Karzinoide to NET

From
Karzinoide

To
NET

1973 Isolation and sequencing of “somatotropin-release inhibitor factor”

1978 Use of somatostatin to control carcinoid flushing

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Introduction

Carcinoids are histologically and biochemically diverse tumors

Classification is based on:
- Anatomical location, with carcinoids being more commonly located in the ileum
- Embryologic origin: Foregut, Midgut, and Hindgut Carcinoid

WHO classification published in 2000:
- Neuroendocrine tumor instead of carcinoid
WHO Histological Typing of Neuroendocrine Tumors

1. Well differentiated neuroendocrine tumor
   - Benign or low grade malignant
   - Mucosa-Submucosa, <1-2cm

2. Well differentiated neuroendocrine carcinoma
   - Low grade malignant
   - Muscularis propria or beyond, or metastasis

3. Poorly differentiated endocrine (small cell) carcinoma
   - High grade malignant

Table 7. Criteria for assessing the prognosis of neuroendocrine tumors of the gastrointestinal tract

<table>
<thead>
<tr>
<th>Biological behavior</th>
<th>Metastases</th>
<th>Invasion of m. propria*</th>
<th>Histological differentiation</th>
<th>Tumor size</th>
<th>Angioinvasion index</th>
<th>Ki-67 syndrome</th>
<th>Hormonal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign</td>
<td></td>
<td></td>
<td>Well differentiated</td>
<td>≤1 cm*</td>
<td>-</td>
<td>&lt;2%</td>
<td>-</td>
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<tr>
<td>Benign or low grade malignant</td>
<td></td>
<td></td>
<td>Well differentiated</td>
<td>≤2 cm</td>
<td>+/-</td>
<td>&lt;2%</td>
<td>-</td>
</tr>
<tr>
<td>Low grade malignant</td>
<td>+</td>
<td>+*</td>
<td>Well differentiated</td>
<td>&gt;2 cm</td>
<td>+</td>
<td>&gt;2%</td>
<td>+</td>
</tr>
<tr>
<td>High grade malignant</td>
<td>+</td>
<td>+</td>
<td>Poorly differentiated</td>
<td>Any</td>
<td>+</td>
<td>&gt;30%</td>
<td>-</td>
</tr>
</tbody>
</table>

* Exception: malignant duodenal gastrinomas are usually smaller than 1 cm and confined to the submucosa
* Exception: benign NET of the appendix usually invade the muscularis propria
Small Bowel Carcinoid: Epidemiology

- Data from both the NCDB and the SEER databases
- 67,843 patients with small bowel malignancies
  - 37.4% of patients had carcinoid tumors
  - 36.9% had adenocarcinomas
  - Stromal tumors or lymphomas
- Increase by 4% per year since 1973, surpassing adenocarcinomas as the most common small bowel tumor

Increased incidence of Carcinoid Tumors
US population 1973–2005
Data from SEER database, US National Cancer Institute

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Macroscopic Appearance

- Carcinoids are white, yellow, or gray firm submucosal nodules in the wall of the intestine.

- They may protrude into the lumen as polyps.

- Overlying mucosa may be intact or ulcerated.
The primary lesions are small.

The metastatic deposits in the lymph nodes, mesentery, and liver may be quite large.

Involvement of the subserosa and adjacent mesentery stimulates an intense desmoplastic reaction.
Macroscopic Appearance

Intense desmoplastic reaction results in dense fibrosis that may lead to:

- Mesenteric fibrosis
- Intestinal kinks
- Retraction

Partial or intermittent bowel obstruction
Ischemia and venous congestion when affecting mesenteric vessels
Small Bowel Carcinoid: Microscopy

- Rounded, submucosal, nodular configuration
- Nests of tumor cells in the submucosa with surrounding fibrosis and Infiltrative pattern of growth
- Uniform nuclei and cytoplasmic secretory granules
- Can be identified by silver impregnation staining or by IHC staining for neuroendocrine markers (chromogranins)
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Small Bowel Carcinoid

- Median age of presentation is 66 y/o

- Carcinoids location:
  - ileum in 45%
  - duodenum in 18%
  - jejunum 6%
  - diffuse/ undetermined in the remaining cases

- Multicentric in up to 30% of patients
Small Bowel Carcinoid

- Associated with non-carcinoid neoplasms in up to 29% of patients (17% operated patients, 36% necropsies)
  - 50% are adenocarcinomas of the GI tract

- Tumors located in the duodenum and jejunum are more often adenocarcinomas

- Tumors found in the ileum are more likely to be carcinoids
Clinical Presentation

- Often asymptomatic as they grow slowly in the intestinal wall.

- Initially, symptoms are vague with a long history of episodic abdominal pain that progresses to cramping, abdominal distention, nausea, and vomiting, diarrhea, and weight loss.

- Ultimately, the primary tumor and mesenteric involvement may result in small bowel obstruction, ischemia, or bleeding.
Clinical Presentation

- Exploration for SBO or ischemia: 30% to 50%
- Vague abdominal symptoms
- Detection of liver metastasis on imaging/celiotomy
- Carcinoid syndrome
- Occult GI Bleed
- Other sites of metastasis: bones, lungs, CNS, mediastinal and peripheral lymph nodes, ovaries, breast and skin

October 2006  January 2009
Clinical Presentation: Carcinoid Syndrome

- 20% to 30% of patients with small bowel carcinoid develop signs of carcinoid syndrome:
  - flushing
  - secretory diarrhea
  - palpitations
  - intolerance to some foods or alcohol
  - right-sided valvular heart disease
  - bronchoconstriction

- Associated with the release of various substances from the tumor: Serotonin, histamine, dopamine, vasoactive intestinal peptide, others
Clinical Presentation: Carcinoid Syndrome

- The liver can detoxify substances released by the primary and mesenteric tumors.

- Carcinoid syndrome develops when vasoactive substances produced by the tumor enter the systemic circulation.

- The syndrome most commonly occurs:
  - metastatic involvement of the liver
  - large burden of retroperitoneal tumor involvement
Carcinoid Heart Disease

- 30% of patients with carcinoid syndrome
- Caused by the effects of circulating serotonin
- Characterized by fibrous plaques that preferentially involve the right side of the heart
- Those with left sided disease are likely to have right-to-left cardiac shunts
- May require valve replacement
- Responsible for about 50% of deaths in these patients
Duodenal/Ampullary Carcinoids

- Lower serotoninergic hormone levels than other carcinoids
- When these tumors are >2 cm, they may develop metastases to regional lymph nodes or the liver in 45% of patients
- Approximately 30% may be associated with neurofibromatosis, occasionally MEN I and/or pheochromocytomas
- Should be distinguished from duodenal gastrinomas, particularly in MEN I patients
Diagnosis

30-50% of patients are diagnosed at the time of operation:
- Bowel obstruction
- Ischemia
- Bleeding

Suspected small bowel carcinoid due to GI symptoms, carcinoid syndrome, or incidental imaging findings:
- Biochemical
- Imaging
- Endoscopic Studies
Biochemical Studies: 5-HIAA

- Elevated levels of the serotonin metabolite 5-hydroxy-indolacetic acid (5-HIAA) in 24-hour urine

- 5-HIAA
  - Sensitivity of 73% for localized disease
  - Sensitivity of 100% for metastatic disease
  - Specificity of 100% in predicting the presence of carcinoid
Biochemical Studies: Chromogranin A

- CgA is a glycoprotein released by neuroendocrine tumor cells, measured in the plasma.
- Elevated in >80% of patients with carcinoid tumors but its specificity is low for small bowel carcinoids.
- False positive:
  - proton pump inhibitors, atrophic gastritis, renal impairment, or inflammatory bowel disease.
- There is a correlation between CgA levels, tumor load, and prognosis.
- CgA measurement is currently being used as a tumor marker for monitoring of disease progress and surveillance of recurrence.

Small Bowel Carcinoid: Imaging Studies

- GI contrast studies: UGI, SBFT, enteroclysis
- CT scan
- Nuclear Medicine
  - SPECT
  - PET
- MRI
- EUS
Imaging Studies

- Primary small bowel carcinoid are often small, and typically not seen on GI contrast studies or CT scan.
- CT scan may identify involvement of the mesentery and/or liver.
- A mesenteric tumor with radiating densities is highly suggestive of mesenteric metastasis of small bowel carcinoid.
- Calcifications present in more than 50% of those lesions.
Abdominal Computed Tomography Scan
Illustrating a Mesenteric Tumor with Radiating Densities and Calcifications
Imaging Studies: CT Scan

- Relationship to major mesenteric vessels
- Define the extent of liver involvement
- Liver metastases are hypervascular
- Tumor necrosis may produce central, non-enhancing regions, giving lesions a rim-like enhancement
- MRI may better demonstrate the extent of liver metastasis
Abdominal Computed Tomography Scan: Liver Metastases From Small Bowel Carcinoid
**Somatostatin Receptor Scintigraphy (SRS)**

- Small bowel carcinoids overexpress somatostatin receptors which have high affinity for octreotide.
- Octreoscan is used to determine metastatic disease.
- 90% sensitivity.
- Change management:
  - 19%-33% of patients.

*Ahlman, Semin Oncol 1994;21:21-28
Schillaci, J Nucl Med 2003;44:359-368*
New Imaging Modalities

- Standard $^{18}$FDG-PET is less helpful in the setting of well-differentiated tumors.
- NET’s take up decarboxylate amine precursors (APUD) such as $^{11}$C-labeled and $^{18}$F-labeled serotonin and levodopa.
- Spatial resolution of PET is better than SRS-SPECT (3-fold, 0.5 cm vs. 1-1.5 cm).
- These studies have better sensitivity for primary tumors and lymph node, pleural and bone metastasis.

Comparison of $^{68}$Ga-DOTATOC PET and $^{111}$In-DTPAOC (Octreoscan) SPECT in patients with neuroendocrine tumours

- PET can be performed 1 hr after injection vs. 4-6h, 24h, 48h after tracer injection for SRS
- PET had improved identification, in particular, for skeletal and lung manifestations*
- Quantification SUVs, may have a role in selection of patients for radionuclide treatment

$^{18}$F-DOPA PET scan: Liver and Small Bowel Lesion

Koornstra et al Digestive and Liver Disease; 41, 2009
Endoscopic Studies: Localization of the Primary Tumor

**Duodenal carcinoids:**
- EGD
- Endoscopic ultrasound (EUS) to determine the extent of disease/lymph node involvement

**Ileo-colonoscopy:**
- Rule out synchronous neoplastic disease
- May identify carcinoid tumors in the terminal ileum/ileocecal valve
Capsule Endoscopy

- May be useful after small bowel enteroclysis studies have failed to detect the primary tumor.
- It can be used to screen the small bowel in patients with suspected small bowel carcinoid.

![Image of capsule endoscopy devices with dimensions: 26.3 mm and 11.4 mm]
Double Balloon Enteroscopy

- DBE can be performed through the oral and/or the anal route
- The combined approach allows for complete small bowel examination in 86% of patients
- DBE allows for direct access to the lesion for histological diagnosis for India ink marking for intraoperative localization
DBE: Small Bowel Carcinoid

- Detection of primary tumors when US, CT, EGD, ileocolonoscopy unable to detect
- 17 DBE in 12 patients
- Submucosal tumor ileum or jejunum in 7 patients (58%)
- 6/7 patients underwent resection
- Only in 4 disease was confirmed/2 patients false positive
- DBE to be performed in selected cases, possibly based on a positive previous workup

Bellutti et al, Dig Dis Sci 54, 2009
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Treatment

- Multidisciplinary effort
- Surgical therapy is the primary treatment for most patients
- Specific issues in the pre-operative assessment of patients with small bowel carcinoid:
  - Determination of the extent of local and distant disease
  - Identification of synchronous carcinoid and non-carcinoid tumor
  - Fluid and electrolyte repletion
  - Detection of cardiac abnormalities
  - Pharmacological treatment of carcinoid syndrome
Pharmacological Treatment of Carcinoid Syndrome

The risk of carcinoid crisis is higher for patients with carcinoid syndrome, but all patients are at risk.

Prophylactic measures:
- Perioperative administration of octreotide (100mcg Subcutaneously TID)

Carcinoid crisis:
- Bolus intravenous octreotide (100mcg IV push) followed by infusion
- Antihistamines, hydrocortisone, and albuterol as needed
Treatment: Duodenal/Ampullary NET

- <1cm lesions may be locally treated by endoscopic resection, provided that there is no evidence of lymph node involvement* by imaging, SRS, and ideally, EUS.

- Lesions between 1 and 2 cm and periampullary lesions may be amenable to transduodenal excision; the concern again is for retained lymph node metastases*.

- Large, >2 cm duodenal carcinoids or lesions with associated lymph node involvement should be treated by duodenal resection which most often requires pancreaticoduodenectomy.

*LN metastasis may not correlate well with size of the tumor.
Pancreaticoduodenectomy: LN involvement

Transduodenal Excision

Pancreaticoduodenectomy: LN involvement
Treatment: Jejunal/Ileal Carcinoids

- Inspection for synchronous lesions
- The primary tumor and mesenteric metastases should be removed by wedge resection of the mesentery and limited intestinal resection
- Median survival increased from 4 to 7.4 years

Hellman, WJS, 2002;26
Treatment: Jejunal/Ileal Carcinoids

- Emergency operation → re-operation as needed after the patient has been evaluated
- In cases of severe desmoplastic reaction around the superior mesenteric vessels, radical resection may not be possible
- Wedge resection in the fibrotic and contracted mesentery may compromise the superior mesenteric vessels and de-vascularize a large extent of small bowel leading to short bowel syndrome
Resection of Terminal Ileum Primary Tumor and Mesenteric Metastasis

- Mesenteric tumor may extensively involve the mesenteric root
- Mobilization of cecum, TI, and mesenteric root allows the tumor to be lifted, separated from duodenum, pancreas and mesenteric vessels
- Preservation of intestinal vascular supply and intestinal length

From Åkerström et al, Best Pract Res Clin Gastroenterol 19:5, 717, 2005
Treatment: Small Bowel Carcinoids

- Intestinal resection should be reserved until dissection of the mesenteric tumor is complete in an effort to determine bowel viability.
- Tumor multicentricity should not be a contraindication for resection.
- In asymptomatic patients, prophylactic resection of mesenteric tumor is recommended as it may later become more difficult to manage.
- Cholecystectomy should be considered as many patients on long term somatostatin analogs will develop gallstones.
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Treatment of Metastatic Disease to Liver

- >60% will have non-localized disease at diagnosis
- 50% will present with liver metastases
- Surgical resection remains the gold standard
- The European Neuroendocrine Tumor Society (ENETS) has established minimal requirements for resection with curative intent:
  - 1) resectable well-differentiated liver disease with acceptable morbidity (close to 30%) and <5% mortality
  - 2) absence of right heart insufficiency
  - 3) absence of extra-abdominal metastases or diffuse peritoneal carcinomatosis

Steinmuller et al Neuroendocrinology 2008;87:47-62
Treatment of Metastatic Disease to Liver

- Survival rate of 60-80% at 5 years for patients resected for cure

- Primary tumor should be removed with one or two-step procedures

- If heart surgery is also required, it should be undertaken first, about 3 months prior to liver resection
Treatment of Metastatic Disease to Liver: Options for Unresectable Disease

- Ablative procedures (RFA and cryotherapy)
- Trans-catheter arterial embolization or chemoembolization (TACE):
  - Objective tumor responses can be seen in over 50% of patients as well as effective control of symptoms
- Molecular targeted radionuclide therapy
- Palliative debulking procedures for functional symptoms that don’t respond to medical treatment
- Liver transplantation may be an option in very well selected candidates
Biotherapy: Long-acting somatostatin analogs

- Effective in reducing hypersecretion related symptoms in patients with carcinoid syndrome

- A reduction of biochemical markers can be seen in 40-60% of patients and symptomatic improvement in 40-80%

- The anti-proliferative effect of somatostatin analogs is limited with partial or complete responses seen in less than 10% of patients

- Stabilization of progression of disease occurs in 24-57% of patients with documented tumor growth before initiation of treatment
Biotherapy: Long-acting somatostatin analogs

- Therapy is initiated with short-acting analogues, followed by depot formulations that can be given every 4 weeks.

- Side effects:
  - Abdominal discomfort
  - Steatorrhea
  - Malabsorption
  - Gallstone formation

- Monitoring: Symptoms, urinary 5-HIAA
Biotherapy: Interferon-\(\alpha\)

- Interferon-\(\alpha\) treatment is recommended as second-line treatment of functioning tumors with a low proliferation rate.

- Effect is not as rapid and its toxicities are more pronounced than those of somatostatin analogs.

- Biochemical and symptoms control can be seen in up to 50% of patients.

- Partial tumor size responses of 10-15%.
Treatment Approach to Liver Metastases without Extrahepatic Metastasis

RFA = radiofrequency ablation; RPVE = right portal vein embolization; RPVL = right portal vein ligation; LITT = laser-induced thermotherapy; TACE = trans-catheter arterial chemoembolization; TAE = trans-catheter arterial embolization.

Peptide-Receptor Radionuclide Therapy (PRRT)

- Targeting of somatostatin receptors with radiolabeled somatostatin analogs is a promising option for the treatment of somatostatin-receptor-positive endocrine tumors.
- Patients with metastatic or inoperable disease.
- Treatment with somatostatin analogs labeled with $^{111}\text{In}$, $^{90}\text{Y}$ or $^{177}\text{Lu}$ can result in symptomatic improvement.
Peptide-Receptor Radionuclide Therapy (PRRT)

- Tumor remission is seldom achieved with $^{111}$In-labeled analogs

- Objective response with $^{90}$Y (yttrium)-DOTATOC:
  - 9–33%
  - Median duration of response of 30 months

- Objective response to $^{177}$Lu (Lutetium)-octreotate:
  - 29%; stable disease was present in 35% and progressive disease in 20% of patients
  - Median duration of response of 40 months

- Treatment with $^{177}$Lu-octreotate seems to confer a survival benefit of several years
PRRT: ENETS Consensus Guidelines

Eligibility
- Tumor uptake on octreoscan
- Inoperable disease
- Life expectancy at least 3-6 month
- Performance status

Contraindications
- Pregnancy/lactation
- Renal impairment Cr Cl <40-50
- Hgb<8 g/dl, platelets<75K, WBC<2K
- Severe hepatic impairment, TB>3, alb <3, increased PT
- Severe cardiac impairment

Kwekkeboom et al, Neuroendocrinology, 90, 2009
Peptide-Receptor Radionuclide Therapy (PRRT)

- Predictive factors for tumor remission:
  - High tumoral uptake of radioactivity on SRS, PET
  - Limited numbers of liver metastases

- Adverse effects of PRRT are few and mostly mild with the use of renal protective agents

- Serious, delayed adverse effects, such as myelodysplastic syndrome or renal failure, are rare
Improved tumor uptake of $^{177}$Lu-octreotate versus that of $^{111}$In-octreotide
# Tumor Responses in Patients With GEPNETs, Treated With Different Radiolabeled Somatostatin Analogues

<table>
<thead>
<tr>
<th>Center (Reference)</th>
<th>Ligand</th>
<th>No of Patient</th>
<th>CR</th>
<th>PR</th>
<th>MR</th>
<th>SD</th>
<th>PD</th>
<th>CR + PR</th>
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<tbody>
<tr>
<td>Rotterdam⁵</td>
<td>[¹¹¹In-DTPAOctreotide]</td>
<td>26</td>
<td>0</td>
<td>0</td>
<td>5 (19%)</td>
<td>11 (42%)</td>
<td>10 (38%)</td>
<td>0%</td>
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<tr>
<td>New Orleans⁷</td>
<td>[¹¹¹In-DTPAOctreotide]</td>
<td>26</td>
<td>0</td>
<td>2 (8%)</td>
<td>NA</td>
<td>21 (81%)</td>
<td>3 (12%)</td>
<td>8%</td>
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<tr>
<td>Basel⁸ and [⁹⁰Y-DOTA°,Tyr³]octreotide</td>
<td>74</td>
<td>3 (4%)</td>
<td>15 (20%)</td>
<td>NA</td>
<td>48 (65%)</td>
<td>8 (11%)</td>
<td>24%</td>
<td></td>
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<tr>
<td>Basel¹⁰</td>
<td>(⁹⁰Y-DOTA°,Tyr³)octreotide</td>
<td>33</td>
<td>2 (6%)</td>
<td>9 (27%)</td>
<td>NA</td>
<td>19 (57%)</td>
<td>3 (9%)</td>
<td>33%</td>
</tr>
<tr>
<td>Milan¹¹</td>
<td>(⁹⁰Y-DOTA°,Tyr³)octreotide</td>
<td>21</td>
<td>0</td>
<td>6 (29%)</td>
<td>NA</td>
<td>11 (52%)</td>
<td>4 (19%)</td>
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</tr>
<tr>
<td>Rotterdam¹²</td>
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<td>58</td>
<td>0</td>
<td>5 (9%)</td>
<td>7 (12%)</td>
<td>33 (61%)</td>
<td>10 (19%)</td>
<td>9%</td>
</tr>
<tr>
<td>Rotterdam¹³</td>
<td>[¹⁷⁷Lu-DOTA°,Tyr3]octreotate</td>
<td>310</td>
<td>5 (2%)</td>
<td>86 (28%)</td>
<td>51 (16%)</td>
<td>107 (35%)</td>
<td>61 (20%)</td>
<td>29%</td>
</tr>
</tbody>
</table>

Chemotherapy

- Combinations of streptozotocin (STZ) + doxorubicin and/or 5-fluorouracil (5-FU), cisplatin + etoposide and dacarbazine

- The benefits and duration of responses to chemotherapy for small bowel carcinoid are very limited
# Chemotherapy vs. PRRT

The table below compares the results of recent chemotherapy reports with treatment with $^{177}$Lu-DOTA, Tyr$^3$ octreotate.

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Tumor Types</th>
<th>No of Patient</th>
<th>PR/CR (%)</th>
<th>Median PFS (mo)</th>
<th>Median OS (Mo)</th>
<th>Study (yr)</th>
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<tr>
<td>STZ + Doxorubicin</td>
<td>PNET</td>
<td>16</td>
<td>6</td>
<td>NA</td>
<td>NA</td>
<td>Cheng and Saltz $^{41}$</td>
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<tr>
<td>Dacarbazine</td>
<td>Carc</td>
<td>56</td>
<td>16</td>
<td>NA</td>
<td>20</td>
<td>Bukowski et al $^{37}$</td>
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<tr>
<td>Dacarbazine</td>
<td>Carc</td>
<td>7</td>
<td>14</td>
<td>NA</td>
<td>NA</td>
<td>Ritzel et al $^{38}$</td>
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<td>FU + IF-A</td>
<td>Carc/PNET</td>
<td>24</td>
<td>21</td>
<td>8</td>
<td>23</td>
<td>Andreiev et al $^{39}$</td>
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<td>Mitoxantrone</td>
<td>Carc/PNET</td>
<td>30</td>
<td>7</td>
<td>NA</td>
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<td>Nejti et al $^{40}$</td>
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<td>Paclitaxel</td>
<td>Carc/PNET</td>
<td>24</td>
<td>4</td>
<td>3</td>
<td>18</td>
<td>Ansell et al $^{42}$</td>
</tr>
<tr>
<td>STZ + FU + Doxorubicin</td>
<td>PNET</td>
<td>84</td>
<td>35</td>
<td>15</td>
<td>37</td>
<td>Kroupárák et al $^{47}$</td>
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<tr>
<td>Doxorubicin + FU</td>
<td>Carc</td>
<td>85</td>
<td>13</td>
<td>5</td>
<td>16</td>
<td>Sun et al $^{48}$</td>
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<tr>
<td>STZ + FU</td>
<td>Carc</td>
<td>79</td>
<td>15</td>
<td>5</td>
<td>24</td>
<td>Sun et al $^{49}$</td>
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<td>Irinotecan + FU</td>
<td>Carc/PNET</td>
<td>20</td>
<td>5</td>
<td>5</td>
<td>15</td>
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<tr>
<td>Oxaliplatin + Capecitabine</td>
<td>Well differentiated</td>
<td>27</td>
<td>30</td>
<td>NA</td>
<td>40</td>
<td>Bajetta et al $^{46}$</td>
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<tr>
<td>Temozolomide</td>
<td>Carc/PNET</td>
<td>36</td>
<td>14</td>
<td>NA</td>
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<td>Ekeblad et al $^{51}$</td>
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<tr>
<td>$^{177}$Lu-octreotate</td>
<td>Carc/PNET</td>
<td>310</td>
<td>30</td>
<td>32</td>
<td>46</td>
<td>Kwekkeboom et al $^{3}$</td>
</tr>
</tbody>
</table>

STZ, streptozotocin; FU, 5-fluorouracil; IF-A, interferon-alpha; PNET, pancreatic neuroendocrine tumor; Carc, carcinoid; PFS, progression-free survival; OS, overall survival; NA, not available. (Adapted from Kwekkeboom DJ et al $^{19}$)

Overall survival in patients from observational and interventional studies (blue bars) and in similar patients with regard to tumor type and disease stage treated with $[^{177}\text{Lu}-\text{DOTA}0, \text{Tyr}3]\text{octreotate}$ (red bars).

- Survival benefit of 40-72 months in patients treated with $[^{177}\text{Lu}-\text{DOTA}0, \text{Tyr}3]\text{octreotate}$

Small Bowel Carcinoid

- Introduction, History, Epidemiology
- Macroscopic and Microscopic Appearance
- Clinical Presentation and Diagnosis
- Treatment of Primary
- Treatment of Advanced/Metastatic
- F/U and Prognosis
CgA: Recurrent Disease Surveillance

- 56 patients radically resected small bowel carcinoid
- CgA, 5HIAA, radiologic examinations 1-3 times/year
- 33/56 patients recurred, median 32 months (range 6-217)
- CgA was the first marker to become elevated in 28/33 (85%)
- CgA continued to be elevated for a median of 30 months before radiologic confirmation

Suggested surveillance for recurrence in asymptomatic patients:
- CgA twice per year
- US or CT annually

CgA and Prognosis

- There is a correlation between chromogranin A levels, tumor load, and prognosis
- 252 patients with midgut carcinoid
- Poor prognostic factors

<table>
<thead>
<tr>
<th>Univariate</th>
<th>Multivariate</th>
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<tbody>
<tr>
<td>Age</td>
<td>Age</td>
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<tr>
<td>CgA (&gt;5000ug/L)</td>
<td>CgA (&gt;5000ug/L)</td>
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<tr>
<td>&gt;5 liver metastasis</td>
<td></td>
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<tr>
<td>Carcinoid Syndrome</td>
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</table>

Janson et al, Ann Oncol 1997;8:685-690
Small Bowel Carcinoid: Prognostic Factors

- 258 patients with small bowel carcinoid
- Overall 5-year survival: 72%
  - Localized disease 94%
  - Regional disease 85%
  - Liver metastasis 63%

Therapeutic algorithm for gastrointestinal neuroendocrine tumors (NETs)

En bloc resection of primary and lymphatic drainage

Liver Metastases
Residual disease

Embolization +/- chemo
Resection
Ablation/ RFA/Cryo
Liver transplant

Pharmacotherapy: SST analogues, Interferon
PRRT
Cytotoxics: 5-FU, STZ, dacarb, others

Follow-up: CgA
Octreoscan CT/MRI
5 HIAA

No metastases
Recurrence
Local
Resection
Liver transplant
Recurrence
Resection

Liver Metastases
Residual disease

5-year overall survival from carcinoids at all sites, carcinoids of the digestive system, and carcinoids of the small intestine, US population 1973–2002
Data from SEER database, US NCI

70%

Requirements for an improvement in NET outcome

- Refinement of universal classification and grading system
- Elucidation of cell biology, development of cell lines and animal models
- Identification of serum markers for early diagnosis
- Development of molecular pathological profiling to define prognosis
- Precise identification of topographic information
- Identification of molecular therapeutic targets
- Development of improved treatment for residual disease
- Establishment of centers of excellence and multidisciplinary teams
- Construction of central clinical and tissue databases
- Government focus on clinical and research funding for an orphan disease
EC-cell carcinoid of the distal ileum in a 45-year-old woman who complained of crampy abdominal pain
Multifocal ileal carcinoids with intussusception in a 43-year-old woman who complained of abdominal pain and nausea
Figure 13a. EC-cell small bowel carcinoid in a 59-year-old woman who complained of a 4-year history of flushing and diarrhea
EC-cell carcinoid of the ileum in a 50-year-old man with abdominal pain
Siegfried Oberndorfer (1876-1944) (top left) presented his observations of multiple “benign carcinomas” (Karzinoide) of the small bowel at the German Pathological Society meeting of 1907 in Dresden (top).

P. Masson and A. Gosset (bottom left and right, respectively) demonstrated the argentaffin staining properties of appendiceal carcinoid tumors in 1914 and suggested that gut enterochromaffin (EC) cells (lower left; bottom right) formed a diffuse endocrine organ. In 1928, they described these cells to be neural in origin and proposed them as progenitors of neuroendocrine tumors of the gut (carcinoids).

The first description of the diffuse neuroendocrine system (DNES) was provided in 1938 by F. Feyrter (bottom), who described argentaffin or argyrophil “clear cells” (“Helle Zellen”) in the gut and pancreas and proposed that such cells produced hormones that acted locally.
Case Study #1
Submucosal Mass

History: 72-year old woman, unexplained iron deficiency anemia. Hgb 10, MCV 82, RDW 13. Three cards for FOBT all positive.

History of note for Gaucher’s with known platelet dysfunction

Normal EGD and colonoscopy 4 months earlier

Family history of celiac disease
PillCam Capsule Findings
Submucosal Mass
Conclusion

- Capsule endoscopy shows multiple submucosal masses. Some are ulcerated and bleeding. These are located in the mid-small bowel. A preresumptive diagnosis of multicentric carcinoid is made.

- A CT scan is negative as is an octreotide scan.

- The patient undergoes surgery guided by intraoperative endoscopy. Multiple carcinoid tumors are discovered and a mid-small bowel resection is performed.
Small Bowel Carcinoid: Epidemiology
Macroscopic Appearance: Desmoplastic Reaction
Ileal carcinoid that was discovered incidentally in a 67-year-old woman who underwent preoperative CT for endometrial carcinoma.
Additional Imaging

Echocardiogram should be performed in patients with carcinoid syndrome to evaluate for valvular disease and congestive heart disease.
Treatment of Metastatic Disease to Liver: Other Options

- These techniques can be used effectively as anti-tumor treatment and in relieving symptoms in patients with liver metastases either as sole therapy or in combination with resection.
- RFA has the potential to be delivered percutaneously under image guidance, which may be useful for non-operative candidates.
- The use of RFA is not recommended for patients with tumors over 5 cm or near vital structures, large vessels and central bile ducts.
Clinical Presentation: Bowel Obstruction

October 2006

January 2009
TABLE 5. Classification of neuroendocrine tumors of the ileum, cecum, colon, and rectum

1. Well-differentiated neuroendocrine tumor (carcinoid)
   - Benign: nonfunctioning, confined to mucosa-submucosa, nonangioinvasive, 
     ≤1 cm (ileum) or ≤2 cm (colon-rectum)
   - Serotonin-producing tumor
   - Enteroglucagon-producing tumor
   - Benign or low grade malignant (uncertain malignant potential): nonfunctioning,
     confined to mucosa-submucosa, angioinvasive, or <1 cm (ileum) or
     <2 cm (colon-rectum)
   - Serotonin-producing tumor
   - Enteroglucagon-producing tumor

2. Well-differentiated neuroendocrine carcinoma (malignant carcinoid)
   - Low grade malignant: invasion of the muscularis propria or beyond, or
     metastases
   - Nonfunctioning or functioning serotonin-producing carcinoma (with carci-
     noid syndrome)
   - Nonfunctioning enteroglucagon-producing carcinoma

3. Poorly differentiated neuroendocrine carcinoma
   - High grade malignant
Small Bowel Carcinoid: Microscopy
Potential side-effects of PRRT, deduced from the normal distribution of radioactivity during diagnostic somatostatin receptor imaging.

- No important effect on pituitary function
- No important effect on thyroid function
- Common: mild bone marrow suppression
- Common: Lymphocytopenia
- Rare: MDS, Leukemia
- Rare: Kidney impairment
- Rare: Liver toxicity
Treatment Response for Gastrointestinal NET

Radiofrequency, cryoablation, and chemoembolization of liver metastases.
PRRT=peptide receptor radionuclide therapy. HL=human leucocyte interferon

Treatment: Duodenal Carcinoids

- Should be removed unless:
  - widely metastatic disease, markedly limited life expectancy or increased surgical risk even in the face of metastatic disease,

- May be resected when present with complications
  - uncontrollable bleeding
  - liver only, potentially resectable metastases

- There are different options for resection, and there is still considerable controversy on the selection of treatment modalities for these lesions
Methods for identification of primary and metastatic GEP-NET: Data pooled from 41 studies