ENDOLUMINAL APPROACH FOR THE MANAGEMENT OF GASTROINTESTINAL CARCINOID

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INTRODUCTION

- Neuroendocrine cells are widely distributed in the body.
- Neuroendocrine neoplasms are defined as epithelial tumors with predominantly neuroendocrine differentiation.
- Can arise in most organs.
- While some clinical and pathological features are unique to the site of origin, other characteristics are shared regardless of the site.
CLASSIFICATION OF NEUROENDOCRINE TUMORS

Gastropancreatic Neuroendocrine Tumors

Well Differentiated
- These were traditionally referred to as Carcinoid & Pancreatic neuroendocrine (islet cell) tumors.
- Generally have a much better prognosis
- Although carcinoids and pancreatic NETs have a similar histologic appearance, they have a different pathogenesis and biology.

Poorly Differentiated
- They are high grade carcinomas which resemble small and large cell neoplasms of the lung
- They are generally more aggressive.
EMBRYONIC CLASSIFICATION OF NETs/
CLASSIFICATION OF NETs BY LOCATION

FOREGUT-
- Stomach carcinoids-
  - Type-1
  - Type-2
  - Type-3
- Lung/bronchial carcinoids

MIDGUT-
- Jejunoileal
- Appendix

HINDGUT-
- Colon
- Rectum


**EPIDEMIOLOGY**

- Carcinoids are relatively rare tumors. As per the SEER analysis of 35,618 tumors, the age adjusted incidence of non-pancreatic primaries is 4.6 per 100,000.

- Annual incidence rate for African Americans is slightly higher than for Caucasians (6.46 v/s 4.6 per 100,000).

- Incidence for males was slightly higher than females 4.97 v/s 4.49 per 100,000.

- The median age for diagnosis of neuroendocrine tumors is 63 years.

- The incidence of neuroendocrine tumors is rising in the US and other parts of the world. Though, this rise can be attributed to increased diagnosis on radiographic imaging and endoscopy.
DISTRIBUTION OF CARCINOID TUMORS

- GI-Tract (55%)
  - Small intestine (45%; mostly in the ileum)
  - Rectum (20%)
  - Appendix (16%)
  - Colon (11%)
  - Stomach (7%)
- Bronchopulmonary (33%)
<table>
<thead>
<tr>
<th>Differentiation</th>
<th>Grade</th>
<th>Traditional</th>
<th>ENETS, WHO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Well-differentiated</td>
<td>Low grade (G1)</td>
<td>Carcinoid, Islet cell, pancreatic (neuro)endocrine tumor</td>
<td>Neuroendocrine tumor, Grade 1</td>
</tr>
<tr>
<td></td>
<td>Intermediate grade (G2)</td>
<td>Carcinoid, atypical carcinoid, islet cell, pancreatic (neuro)endocrine tumor</td>
<td>Neuroendocrine tumor, Grade 2</td>
</tr>
<tr>
<td>Poorly differentiated</td>
<td>High grade (G3)</td>
<td>Small cell carcinoma</td>
<td>Neuroendocrine carcinoma, Grade 3, small cell</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Large cell neuroendocrine carcinoma</td>
<td>Neuroendocrine carcinoma, Grade 3, large cell</td>
</tr>
<tr>
<td>Differentiation</td>
<td>Grade</td>
<td>Mitotic count*</td>
<td>Ki-67 index†</td>
</tr>
<tr>
<td>-----------------</td>
<td>-------------</td>
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<td>--------------</td>
</tr>
<tr>
<td>Well-differentiated</td>
<td>Low grade  (G1)</td>
<td>&lt;2 per 10 HPF</td>
<td>&lt;3%</td>
</tr>
<tr>
<td></td>
<td>Intermediate grade (G2)</td>
<td>2 to 20 per 10 HPF</td>
<td>3 to 20%</td>
</tr>
<tr>
<td>Poorly differentiated</td>
<td>High grade (G3)</td>
<td>&gt;20 per 10 HPF</td>
<td>&gt;20%</td>
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</table>

ENETS: European Neuroendocrine Tumor Society; WHO: World Health Organization.
* Counted in 10 high power fields (HPF), 10 HPF = 2 mm², at least 40 fields (at 400x magnification) evaluated in areas of highest mitotic density. Cut-offs per American Joint Commission on Cancer Staging Manual, 7th edition.
Δ The term "atypical carcinoid" only applies to intermediate-grade NETs of the lung.
A total of three nodular appearing lesions were seen in the body of the stomach, measuring between 5 by 5 mm to 15 by 5 mm. Two had small ulcerations (arrows), which were presumably the site of bleeding. Image A represents a frontal view and image B is during retroflexion.

*Courtesy of Andres Gelrud, MD.*
# GASTRIC CARCINOIDS

<table>
<thead>
<tr>
<th>Types</th>
<th>Malignant Potential</th>
<th>Focality</th>
<th>Disease Associations</th>
<th>Serum Gastrin</th>
<th>Functional Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type-1 (70-80% of cases)</td>
<td>Usually benign</td>
<td>Usually &lt;1cm</td>
<td>Chronic atrophic gastritis and pernicious anemia</td>
<td>Elevated</td>
<td>Usually non-functional</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Multifocal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Appear as polypoid lesions with small central ulceration</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type-2 (5% of cases)</td>
<td>Usually indolent</td>
<td>Frequently multifocal</td>
<td>Gastrinomas/ZE S</td>
<td>Elevated</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>MEN-1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type-3 (20% of cases)</td>
<td>Local or hepatic mets usually present in 65% of patients who come for resection</td>
<td>Solitary</td>
<td>Sporadic</td>
<td>Usually normal</td>
<td></td>
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</tbody>
</table>
**TYPE-1 GASTRIC CARCINOID**

Chronic atrophic gastritis

Autoantibodies towards parietal cells

Achlorhydria

Increased Gastric pH & Gastrin

ECL cells develop into carcinoids (due to high gastrin)

Endoscopic picture of the gastric corpus in a patient with pernicious anemia demonstrates multiple polypoid masses that were shown to be carcinoids, type I.

TYPE-2 GASTRIC CARCINOIDS

Gastrinoma/ZES

High serum Gastrin

Chronic stimulation of ECL cells

Development of carcinoid tumors
Figure 2 Subject A: A polypoid carcinoid lesion at the gastric fundus site about 0.8 cm with typical yellowish color of the lesion; B: A submucosal carcinoid lesion at the duodenal bulb about 1.7 cm; C: A carcinoid tumor with ulceration, at the antrum site, about 4.0 cm in size.
Figure 7. Gastric neuroendocrine tumor. (A) A small gastric carcinoid with surface ulceration seen on retroflexion in the distal body. (B) Merging nests of ECL cells arranged in cords in the deeper part of carcinoids are characteristic of carcinoid tumors. (C)...

Yasser H. Shaib, Massimo Rugge, David Y. Graham, Robert M. Genta

Management of Gastric Polyps: An Endoscopy-Based Approach

Clinical Gastroenterology and Hepatology, Volume 11, Issue 11, 2013, 1374–1384

http://dx.doi.org/10.1016/j.cgh.2013.03.019
DIAGNOSTIC EVALUATION OF GASTRIC CARCINOIDs

Gastric Carcinoid

- EGD
- Gastric biopsy
- Serum Gastrin levels
- Consider gastric pH

Increased Gastrin levels (Type-1 or 2)

High Gastric pH
Type-1 (Atrophic Gastritis)

- Multiphasic CT or MRI
- EUS
- Consider somatostatin receptor scintigraphy

Low Gastric pH
Type-2 (ZES)

- Serum Vitamin B12
- EUS

Normal Gastrin levels (Type-3)

- Multiphasic CT or MRI
- EUS
- Consider somatostatin receptor scintigraphy
### PRIMARY TREATMENT-LOCOREGIONAL GASTRIC CARCINOIDS

<table>
<thead>
<tr>
<th>Type-1</th>
<th>Type-2</th>
<th>Type-3</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Annual endoscopic surveillance and endoscopic resection of prominent tumors</td>
<td>- Resect the primary gastrinoma</td>
<td></td>
</tr>
</tbody>
</table>
| - Consider antrectomy if gastric tumors increase significantly in size or number | - If primary not resected-  
  ➢ Consider endoscopic surveillance and endoscopic resection of prominent tumors and/or  
  ➢ Octreotide or Lanreotide | - If no evidence of lymphadenopathy on EUS consider endoscopic or surgical wedge resection  
  OR  
  ➢ Radical resection with lymphadenectomy |

Adapted from NCCN Guidelines Version 2.2016
HINDGUT CARCINOIDs

**COLON CARCINOIDs**
- Usually detected in patients in their 70s during evaluation for diarrhea, abdominal pain, anorexia, weight loss.
- They are usually non-functional.
- They are more aggressive than rectal carcinoids. 5 year survival rates are 62% across all stages compared with 88% for rectal carcinoids (Modlin, Lye et al. 2003).
- Well differentiated colonic NETs have the worst prognosis of any gastrointestinal tract NET (well differentiated) [1-4]. One reason for more aggressive behavior is that colonic NETs are frequently right sided and may be clinically occult till advanced stages.
- **TREATMENT:** Given that most colonic NETs are >2cm and invading the muscularis propria, they should be managed with formal partial colectomy and regional lymphadenectomy.

**RECTAL CARCINOIDs**
- Most rectal carcinoids are asymptomatic and found incidentally on rectal exam or endoscopy. Most commonly seen in patients in their 60s.
- Most are non-secretory.
- Majority of rectal carcinoids are localized at the time of diagnosis (75-85%).
- Tumor size correlates closely with the likelihood of metastases. 1-4

<table>
<thead>
<tr>
<th>TUMOR SIZE</th>
<th>RISK OF METASTASES (Liver)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1cm</td>
<td>Rarely metastasize</td>
</tr>
<tr>
<td>1-1.9cm</td>
<td>6%</td>
</tr>
<tr>
<td>&gt; 2cm</td>
<td>24%</td>
</tr>
</tbody>
</table>
Most rectal carcinoids are asymptomatic and found incidentally on rectal exam or endoscopy. Most commonly seen in patients in their 60s.

Most are non-secretory.

Majority of rectal carcinoids are localized at the time of diagnosis (75-85%).

Tumor size correlates closely with the likelihood of metastases.

While small rectal NETs are mainly indolent, certain risk factors predict for metastases:

1. Tumor size
2. Depth of invasion (T-stage)
3. Mitotic Index
4. Lymphovascular invasion
Figure - 1 Endoscopic mucosal resection with circumferential incision of a rectal carcinoid tumour. (A) Conventional endoscopic view showing a carcinoid tumour in the rectum; (B) Endoscopic ultrasonography (EUS) image showing the lesion not to invade the muscularis propria layer; (C) Marking dots made around the lesion; (D) Circumferential incision around the dots; (E) Snaring after circumferential incision; (F) Region after endoscopic mucosal resection with circumferential incision; (G) Resected specimen; (H) Histologic view of a rectal carcinoid tumor obtained by endoscopic submucosal dissection (ESD) (H&E stain; ×40).

Naunheim et al reported that the risk of metastases for tumors <2cm was 2% (if confined to the submucosa) and was 48% if the tumor invaded the muscularis propria.

Some recent reports have also implicated Lymphovascular invasion and Mitotic index to be associated with a poor prognosis.
### TNM staging carcinoid tumors of the colon and rectum

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

<table>
<thead>
<tr>
<th>Regional lymph nodes (N)</th>
<th>NX</th>
<th>N0</th>
<th>N1</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Regional lymph nodes cannot be assessed</td>
<td>No regional lymph node metastasis</td>
<td>Regional lymph node metastasis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Distant metastases (M)</th>
<th>M0</th>
<th>M1</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No distant metastasis</td>
<td>Distant metastasis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Anatomic stage/prognostic groups</th>
<th>Stage 0</th>
<th>Stage I</th>
<th>Stage IIA</th>
<th>Stage IIIB</th>
<th>Stage IIIA</th>
<th>Stage IVA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tis</td>
<td>N0</td>
<td>T1</td>
<td>T2</td>
<td>T3</td>
<td>T4</td>
<td>Any T</td>
</tr>
<tr>
<td>N0</td>
<td>M0</td>
<td>N0</td>
<td>N0</td>
<td>N0</td>
<td>N0</td>
<td>N1</td>
</tr>
<tr>
<td>M1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Any N</td>
</tr>
<tr>
<td>M1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>M1</td>
</tr>
</tbody>
</table>

**Note:** cTNM is the clinical classification, pTNM is the pathologic classification.

*Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the AJCC Cancer Staging Manual, Seventh Edition (2010) published by Springer New York, Inc.*
DIAGNOSTIC EVALUATION OF RECTAL CARCINOIDs

RECTAL CARCINOIDS

T1
- EUS
- Endorectal MRI

T2-T4

RECOMMENDED
- EUS and/or Endorectal MRI
- Abdominal/Pelvic multiphasic CT/MRI
- Colonoscopy

AS NEEDED
- Somatostatin receptor scintigraphy
- Chest CT
- Biochemical evaluation

Adapted from NCCN Guidelines Version 2.2016
TREATMENT OF RECTAL NETs
[TREATMENT MODALITIES]

- Conventional endoscopic resection
  1) Standard polypectomy

- Advanced endoscopic resection
  1) Endoscopic mucosal resection - EMR
  2) Cap assisted EMR
  3) Endoscopic submucosal dissection
  4) Transanal endoscopic microsurgery [TEM]

- Transanal surgical resection

- Radical resection (low anterior resection [LAR], abdominoperitoneal resection [APR])
TREATMENT OF LOCOREGIONAL RECTAL CARCINOIDS

TUMOR SIZE

< 1cm
- Confined to mucosa or submucosa (T1)

> 2cm
- Invading muscularis propria (T2)

TREATMENT OPTIONS

< 1cm
- Standard endoscopic resection
- Advanced mucosal resection

I prefer
(Greater likelihood of tumor negative margins)

I do not prefer this

> 2cm
- Radical surgical resection (LPR, APR)

Tumors with risk factors like LVI, high mitotic index, size >1.5cm should be treated with surgical resection and those without risk factors can be treated with transanal resection or advanced endoscopic resection.
COMPLETING AN INCOMPLETE RESECTION
SURVEILLANCE OF RECTAL CARCINOIDs

Rectal Carcinoids

T1

<1cm
No follow-up

1-2cm
Endoscopy with rectal MRI or EUS at 6 and 12 months

T2-T4

3-12 months post-resection
- H&P
- Consider multiphasic Ct or MRI
- Biochem evaluation as clinically needed

>1 year post resection up to 10 years
- Every 6-12 months - H&P multiphasic CT/MRI

Based on NCCN guidelines 2.2016
Acknowledgment for assistance: Guneesh S. Uberoi, MD, Research Intern at MDACC

THANK YOU!