Changing Paradigms in Gastrointestinal Neuroendocrine Tumors

J Philip Boudreaux, MD FACS
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<th>n = 1805</th>
<th>Overall Survival from Dx</th>
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# Ochsner/LSU NETS Clinic

## Patient Distribution

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Traditional Teaching

- Neuroendocrine tumors such as carcinoid are slow growing and do not require aggressive management
- Treatment is primarily symptom control
- Somatostatin analogues are the mainstay
- Asymptomatic primaries do not need to be resected
- 5–yr survival reported as 30-50% if metastatic
Lessons Learned

- Review of 84 cases of advanced disease
- 80% survival at 3 years with aggressive management
- Occult intestinal obstruction was present in 32% of patients referred as “terminal”
- 5% of late stage patients could be rendered NOD
- Mesenteric vascular encasement is NOT a contraindication to resection

How Rare is “RARE”

- Neuroendocrine tumors of the GI tract are the most common malignancy after colon cancer
- Bronchial carcinoids are the second most common lung cancer
- Over 100,000 people have NETs right now
Appendiceal Carcinoids

• Majority located at tip
• 10% located at base
• 18% associated with other GI malignancy
• 27.5% invasion or metastasis
• 29% mortality @ 5 years

(Modlin IM, Cancer 2003 Feb 97:934-59)
13,715 Carcinoids
Appendiceal Carcinoids

Metastatic risk increased with:

- Lymphovascular invasion
- Invasion of mesoappendix
- Invasion of base
- Poorly differentiated, high mitotic rate

IF ABOVE: Right hemicolecotomy
Rectal Carcinoid

- 5-year survival
- Local: 90%
- Regional: 49%
- Distant: 26%
Rectal Carcinoid

- Typically silent
- 13% of all GEP NETS, increasing to 27%
- Often SSTR positive (octreoscan)
- Often PSA, CEA, CGA levels increased
- Increased incidence in AA, 5 per 100K
- Increasing in Asian
Midgut Carcinoids

- Syndrome present in 10%
- Multiple tumors in 40%
- Associated malignancies 29%
- Metastasis at diagnosis is common:
  - <1 cm: 12%
  - >1 cm: 70-85%
Unknown Primary

- Asymptomatic vs. symptomatic
- Occult obstruction
- Mesenteric vascular encasement
Metastatic Risk: Classic Teaching

- Size
  - < 1cm: very low risk
  - > 2cm: high risk

- Location
Improved Survival with Resection of Primary in Presence of Liver Metastasis

- Improved progression free survival
- **56 months vs. 25 months** (p<.001)
- Improved median survival
- **159 months vs. 47 months** (p<.001)

(Givi B, Pommier, et. al. Surg 2006 Dec.)
Common Intraoperative Findings

- Partial bowel obstruction
- Massive mesenteric lymphadenopathy
- Mesenteric vascular encasement
- Multiple “primary” tumors
- Liver and extrahepatic metastasis

Boudreaux, P., Putty, F., et al, Surgical Treatment of Advanced Stage Carcinoid Tumors,
Metastases

The primary NETS PARADOX
Clinical Presentation
Cytoreduction

- Decreasing tumor burden to diminish symptoms, prolong life, and/or improve quality of life
- NON-SURGICAL METHODS:
  - Chemo-(or bland) embolization
  - Radioembolization
- SURGICAL:
  - Resections (Laparoscopic or Open)
  - Energy ablations, (Percutaneous, Lap, Open)
  - Transplantation (Single or MVOT)
CHEMOEMBOLIZATION & RADIOEMBOLIZATION
Chemoembolization and Radioembolization

- Limited application outside of the liver
- Radioembolization carries risk of ulcers
- Embolization eventually occludes the artery
- Embolization makes subsequent surgery much more difficult due to intense scar formation
- We prefer to do embolizations after all surgery is completed
RADIOFREQUENCY ABLATION (RFA) & MICROWAVES
RFA

• High energy microwave administered to tumors to “burn” the tumor
• Initially used in 1996-1997
• Microwave ablation more recent
Limitations of RFA and Microwave

- Heat generated can damage adjacent structures:
  - Blood Vessels
  - Bile Ducts
  - Pancreatic Duct
  - Ureter
  - Bladder
  - Bowel
Irreversible Electroporation

- IRE uses extremely high voltage direct current pulses for a fraction of a second (nanosecond) “NanoKnife”
- Electricity punches irreversible holes in cell membranes and the cells die
- Does not destroy the stroma (“tissue skeleton”)
- Does not produce heat
- Can be placed near blood vessels, bile ducts, etc.
New Technology:

- Nanoknife: irreversible electroporation
- Over 50 tumors treated to date
Surgical Cytoreduction

- Open
- Laparoscopic
- Can use blended technologies and a variety of tools
Treatment Procedures
Results Subset: Tumor Involving Mesenteric Root (n=41)

- 50% patients explored elsewhere and declared non-resectable
- Symptoms of mesenteric ischemia and/or small bowel obstruction (SBO)
- 39/41 (95%) were able to be resected
- 37/41 (90%) with a marked improvement in symptoms

Lymphatic Mapping

• Resect tumor(s) with “adequate margins” using lymphatic mapping
• Conservation of bowel length
• Preserve blood supply
• Spare ileo-cecal valve whenever possible, based on lymphatic mapping technique

LYMPHATIC MAPPING OF MIDGUT CARCINOID CAN PRESERVE ILEO-CECAL VALVE
Liver Transplantation

- Indications still not defined
- Presence of extrahepatic disease as contraindication??
- Most NET patients die of liver disease
- Many limitations in availability of organs
- Current distribution system makes transplant of cadaver livers difficult
- Option of living related liver donation, MVOT

Liver Transplantation for the Treatment of Liver Metastases From Neuroendocrine Tumors: An Analysis of the UNOS Database

Case Study:

- 42 year old with 3 year history of flushing and episodic diarrhea
- After diagnosis, began octreotide therapy @ 20mg/mo with mild improvement
- Sought second opinion: “not a surgical candidate, recommend chemotherapy”
• Progression of tumor on clinical trial of chemotherapy after 4 months
• Sought third opinion: “Not a surgical candidate, try Y-90 microspheres”
• Temporary improvement in symptoms,
• Sought fourth opinion: “Get evaluated by an experienced surgeon or go for liver transplant”
Final Pathology:
1 cm moderately well differentiated T1 primary
1/19 nodes positive,
13 cm liver tumor
KI 67 <1%

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<tr>
<td>5-HIAA</td>
<td>16.5</td>
<td>3.4</td>
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<tr>
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A Single Institution’s Experience with Surgical Cytoreduction of Stage-IV, Well-Differentiated, Small Bowel Neuroendocrine Tumors (NETs)

J. Philip Boudreaux MD, FACS¹, Yi-Zarn Wang MD, FACS¹, Anne E. Diebold BS¹, Daniel J. Frey MD, FACS², Lowell Anthony MD³, Ann Porter Uhlhorn RN⁴, Pamela Ryan RN⁴, and Eugene A. Woltering, MD, FACS¹

Ochsner/Louisiana State University Health Sciences Center, New Orleans, LA; ²Louisiana State University Health Sciences Center, Lafayette, LA; ³University of Kentucky Markey Cancer Center, Lexington, KY; ⁴Ochsner Medical Center-Kenner, Kenner, LA
# Carcinoid Symptoms (n=229)

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Mean survival from histologic diagnosis of a NET was 236 months.

Kaplan-Meier survival rates:
- 5-year: 87%
- 10-year: 77%
- 20-year: 41%

5-Year Survival Rates for Patients with Metastatic Small Bowel NETs by Institution

- Olney: Sl- 1984, n=10
- Saha: Sl-1988, n=30
- Modlin: SEER- 1996, n=NR
- Shebani: Sl- 1998, n=NR
- Talamonti: Sl- 1998, n=11
- Schinal: Sl- 2002, n=NR
- Maggard: SEER- 2002, n=40
- Oberg: Sl- 2004, n=284
- Bergstuen: Sl- 2009, n=171
- Boudreaux: SEER- 2010, n=NR
- Woltering: Sl- 2011, n=319

*SI: Single Institutional Study
NR: Not reported
## Survival for Patients with Small Bowel NETs

<table>
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<tr>
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<th>Regional N=68</th>
<th></th>
<th>Distant N= 319</th>
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<tr>
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<td>Median Survival (Months)</td>
<td>3- Year Survival Rate</td>
<td>5- Year Survival Rate</td>
<td>10- Year Survival Rate</td>
</tr>
<tr>
<td>LSUHSC/OMCK</td>
<td>Not yet reached</td>
<td>97%</td>
<td>92%</td>
<td>81%</td>
</tr>
<tr>
<td>SEER (NANETS)</td>
<td>107 mo.</td>
<td>83%</td>
<td>71%</td>
<td>46%</td>
</tr>
<tr>
<td>Difference</td>
<td>------</td>
<td>14%</td>
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\[ p =.004 \quad \text{and} \quad p <.001 \]

Survival Curves From Histological Diagnosis (SEER vs. LSUHSC/OMCK)

Patients with Distant Disease

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Time (months)

Survival probability (%)
Mean Karnofsky Scores

Pre-Op

Post-Op

p < 0.0001

Pre-Op: 65
Post-Op: 85
Conclusions

• A proactive and aggressive surgical approach to the management of this “indolent” disease provides a significant increase in the survival of patients with NETS.
• We feel that a change in treatment philosophy from passive to active and from conservative to aggressive is warranted.
• The survival rates seen in this study are objectively higher than other studies’ survival rates and should prompt future research on the role of cytoreductive surgery in a multidisciplinary clinic setting.

Small Bowel NET Therapies

- Aggressive surgical cytoreduction
- RFA
- Microwave ablation
- Irreversible Electroporation (Nanoknife ablation)

Adjuvant therapies
- Bland or chemoembolization
- $^{90}$Y microsphere embolization
- $^{131}$I MIBG therapy
- Biologic response modifier therapy
- Chemotherapy
- Peptide Receptor Radionucleotide Therapy (PRRT) $^{90}$Y or $^{177}$LU
What A Multidisciplinary Center Can Offer

- Adjunctive Therapies: Clinical trials, MIBG targeted radiotherapy, chemoembolization, radioactive microspheres, liver transplant
- Surgical options for patients with neuroendocrine tumors
- Debulking and search for unknown primary
- Complex liver resections and RFA, Nanoknife
- Resections of tumors encasing mesenteric root
- Radioguided surgery (Neoprobe) for abdomen, pelvis, chest, neck
Things to Consider

- Complex liver resections, mesenteric dissections, and transplantation are not prospective, randomized, nor controlled entities.
- They are extreme examples of “operator dependent” outcomes.
- Non-resectability is a moving target as our technologies and skills accrue.
- High dose octreotide intra-op infusions prevent “carcinoid crisis.”
Things to Consider

- Multidisciplinary RE-evaluation is important over time
- Sequencing and timing of different therapies are critical to success
- Non-resectability may just mean “not resectable right now”

NETS Multidisciplinary TEAM

Center of Excellence
An affiliation of Louisiana State University Health Science Center & Ochsner Medical Center
Kenner Louisiana
Thank you

Rectal Carcinoid

- >1 - 1.5 cms
- Lymphovascular invasion
- Poorly Differentiated, high mitotic index
- Locoregional spread

= TOTAL MESORECTAL EXCISION!