NETs = Carcinoids
Aggressive is Better

Gagandeep Singh, MD, FACS
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Head Hepatobiliary & Pancreatic Surgery
City of Hope National Comprehensive Cancer Center
**Cell Type & Cancer**

**EXOCRINE: ≈ 93%**
- Acinar Cells
- Duct Cells

**Digestive Enzymes**
- Trypsin: Digests Proteins
- Lipases: Digest Fats
- Amylase: Digests Carbohydrates

**ENDOCRINE: ≈ 5%**
- Alpha Cells
- Beta Cells
- Delta Cells
- Others

**Hormones**
- Glucagon
- Insulin
- Somatostatin
- Gastrin, VIP

**Adenocarcinoma**

**Neuroendocrine Ca**
Neuroendocrine Tumors Classification

Neuroendocrine Tumors- Pancreatic

Carcinoid Tumors- Stomach, Small Bowel, ColoRectal

30%

70%
**Neuroendocrine Tumors**

**Pancreatic NETs**
- Gastrinoma
- Insulinoma
- Glucagonoma
- VIPoma
- Somatostatinoma
- Pancreatic polypeptidoma

Like other NETs, pancreatic NETs can also be nonfunctional tumors.

**Other NETs**
- Lungs
- Thymus
- Stomach
- First part of small intestine

**Appendix**
- Second part of small intestine
- Large intestine

**Colon**
- Rectum

*Well- to moderately differentiated NETs of the lung and GI tract can also be referred to as carcinoid tumors.*
5 Fold Increase in NETs over the Past 30 Years

7 fold increase in the last 40 yrs

Age-adjusted Neuroendocrine Tumor Incidence 1973-2012 with Trend Projection Line, SEER 18
California Cancer Registry: Doubled in the Last 10 Years


Alameda
Central coast (1)
Contra Costa
Los Angeles
Marin
Northern CA (6)
Orange
Riverside
Sacramento
San Bernardino/Inyo/Mono (5)
San Diego/Imperial (7)
San Francisco
San Joaquin Valley-S (2)
San Joaquin Valley-N (3)
San Luis Obispo
San Mateo
Santa Barbara
Santa Clara
Ventura
CA Annual mean, all regions
NET Age-adjusted Incidence by County or Region in CA
2000-2011, Trend Lines
Neuroendocrine Tumors - Prevalence

NETs: More Prevalent Than Stomach and Pancreatic Cancer Combined

Vague abdominal symptoms

Primary tumor

Metastases

Flushing

Diarrhea

Death

Time

20 years

Common Misdiagnoses for Abdominal NETs

- 37% IBS/IBD
- 18% Food Intolerance
- 14% Other GI Conditions/Symptoms
- 17% Psychiatric Disorders
- 9% Other
- 5% Menopause

n=101*

* Data based on 147 misdiagnoses. Some patients were given more than 1 incorrect diagnosis.

Missed Symptoms and Late Diagnosis

- Flushing
  - No sweating
  - First sip of alcohol

- Diarrhea
  - Especially nocturnal

- Wheezing

- Irritable bowel syndrome

- Bloating

Anatomic Imaging - CT Scan / MRI

Std

Arterial

Venous

Delayed
ERCP- Endoscopic Ultrasound

**CT & MRI**
The ability to pick up extrapancreatic Dz
Anatomic CT & Indium-111 Pentetreotide/Octreotide Scintigraphy
Tumor Markers

-General NET markers
  - Chromogranin A
    - Affected by somatostatin analogues, proton pump inhibitors, kidney function, liver function
  - Neuron-specific enolase

-Midgut (small bowel, appendix, cecum)
  - 5 HIAA (24-hr urine collection)
  - Serotonin (blood, more variable)

5-HIAA = 5-hydroxyindoleacetic acid
Chromogranin A vs. 5 HIAA

It is more important if the Chromogranin A levels are negative.
Other Markers in Functional Tumors

Fasting measurements when possible

- **Gastrinoma**
  - **Gastrin**

- **Glucagonoma**
  - **Glucagon**

- **Insulinoma**
  - **Insulin**
  - **Pro-insulin**
  - **C-peptide**

- **VIPoma**
  - **Vasoactive intestinal peptide**
Lots of markers; expression can change over time
  - Chromogranin B and C, pancreastatin, substance P, neurotensin, neurokinin A, pancreatic polypeptide

Take large panel of markers at key points
  - Diagnosis or relapse

Follow a few elevated markers over time

Not necessary to check every marker at each visit
Survival Rate as a Function of Extent of Disease

Based on well- and moderately differentiated histology.
Neuroendocrine Tumors: Center of Excellence
@ City of Hope

Surgeon Oncologist

Medical Oncologist

Radiologist- IR

Gastroenterologist

Radiation Oncologist

Nutritionist

Endocrinologist

Research
Genetics
CURRENT TREATMENT APPROACHES

“The first question we ask ourselves is- are the tumors surgically resectable?”

SURGERY IS THE GOLD STANDARD

WHEN POSSIBLE

Somatostatin analogs
mTOR inhibitors
Chemotherapy for pancreatic NETs
Regional therapy approaches
Principles of NET Surgery

- Locate and resect primary p/NET or Carcinoid
  - Imaging & Tumor Markers

- Resect Mesenteric Nodal Masses

- Resecting Liver Metastases

- Remove the Gall Bladder

- Be prepared for Carcinoid Crisis
Operations for Pancreatic NETs

- Whipple Pancreatoduodenectomy ≈65%
  - Classic
  - Pylorus Preserving
- Distal Pancreatectomy with Splenectomy ≈30%
- Central Pancreatectomy
- Total Pancreatectomy ≤ 5%
Pancreatico-Jejunostomy
JG Fortner: 1973 - Regional Pancreatectomy
Extended Pancreatectomy
Hepatic Ar and PV Reconstruction
Primary Carcinoid of the Small Bowel
Small Bowel - NET
Retrospective review of 84 patients with abdominal carcinoids and proven liver mets

60 patients had removal of primary alone

Median PFS 56 months in resected vs. 26 months in unresected  (p<0.001)

Median OS not reached in resected vs. 47 months in unresected  (p<0.001)
Resection of the Primary vs. No Resection

Even if the Liver Mets are left behind

UKINETS Study


Fig. 3. Survival of patients with and without primary tumor resected.

Univariate analysis

Log rank (Mantel-cox) $P < 0.000$

- Primary removed
- Bowel bypass
- Failed resection
- No resection
- Resected

Duration of follow-up from date of diagnosis

0 years 5 years 10 years 15 years 20 years 25 years 30 years
Resection of the Primary vs. No Resection

No distant metastases

- Primary resected
- Primary not resected

With distant metastases

- Both PRIM and METs resected
- METs only
- PRIM only

p < 0.001

Years since diagnosis

Resection of the Primary vs. No Resection

Time to Liver Progression

Overall Survival by Group

Progression Free Survival

Primary not resected
Primary resected

P<0.001

Months of Followup

Primary Not Resected
Primary Resected

5-Yr=21%

47 Months

P<0.001

Months of Follow-up
Resection of the Primary NET

Presented at Society of Surgical Oncology 2016

n= 864 Stage 4
California Cancer Registry

Improves Survival with or without Liver Treatment

OS Gastric without Liver Treatment

\[ p = 0.1329 \]

OS Pancreas without Liver Treatment

\[ p = 0.0002 \]

OS Small Bowel without Liver Treatment

\[ p < 0.0001 \]

OS Colorectal without Liver Treatment

\[ p < 0.0001 \]
Resection of the Primary NET

Implements Survival even MORE with Liver Treatment

OS All Treatment Groups

- No PTR, No LT
- PTR, No LT
- No PTR, LT
- PTR, LT

n= 864 Stage 4 California Cancer Registry

A Lewis, M White......G Singh MD
What Is the TERMINAL Event in NETs?

LIVER FAILURE- from tumor burden

Irresolvable bowel obstruction
Neuroendocrine Tumors

NET Primary with Liver Mets - To Resect or not Resect
Can We and Should We Resect the Primary & Liver Mets?

March 12th, 2007
Resecting Liver Mets for NETs

Survival After Complete Resection
Of the Colorectal Liver Mets

Survival After Incomplete Resection
Of NET Liver Mets

YES
Limited Options for Advanced NETs

- **pNET**
  - Functional
    - Octreotide LAR + chemotherapy
  - Nonfunctional
    - Chemotherapy

- **Carcinoid**
  - Carcinoid syndrome
    - Octreotide LAR
  - Midgut No syndrome
    - No standard
  - Non-midgut No syndrome
    - No standard

Liver Directed Therapies
- Hepatic artery embolization
- Investigational agents
  - (No approved therapies available)

LAR = long-acting release; pNET = pancreatic NET
pNET: Streptozocin-Based Chemotherapy

9-39% Response Rate
5 years later
s/p Distal Pancreatectomy
Radioembolization x2
Liver Metastases- NET- $^{90}$Y microspheres
Maximizing Treatment of Liver Metastases

Overall Survival byTreatment Type

A. Supportive care  
B. Chemotherapy only  
C. Primary resection  
D. Liver resection  
E. Liver-targeted therapy  
F. Multimodal

p<0.0001

n= 3919
California Cancer Registry
Emerging Therapeutic Approaches

✓ Somatostatin receptor
✓ Peptide receptor radiotherapy (PRRT)
✓ Angiogenesis inhibitors
✓ mTOR inhibitors

mTOR = mammalian target of rapamycin
- Somatostatin receptors highly expressed by NETs
  - Targeting SST receptors can provide symptom and disease control

- New targets could change treatment paradigm
  - mTOR, PI3K, VEGF inhibitors
  - Other antiangiogenic agents

- High potential for combinations

*PI3K = phosphoinositide 3-kinase; SST = somatostatin; VEGF = vascular endothelial growth factor*
**Peptide Receptor Radiotherapy (PRRT)**

- Systemic radiotherapy targeting somatostatin receptors

- Compounds vary by isotope and carrier molecule
  
  RR from ($N = 90$): 4.4%-24%

- 177Lu DOTATATE and 90Y DOTATOC: promising results in phase 2 studies

---

177Lu-DOTATATE: 177Lu-1,4,7,10-tetraazacyclododecane-$N,N',N'',N'''$-tetraacetic acid (DOTA), Tyr$^3$-octreotate; 90Y DOTATOC: [90Y-DOTA]-D-Phe1-Tyr3-octreotide.

**177Lu DOTATATE Phase 2 Study**

- N = 504
- 27.8-29.6 GBq in 4 cycles
- Efficacy in 310 pts, NOT ITT
- RR: 30%
- Median TTP: 40 months
- PRRT clearly active; strong need for rigorous phase 3 study - in progress

**ITT** = intent-to-treat; **RR** = response rate; **TTP** = time to progression

Imaging studies property of James Yao, MD.
CONCLUSIONS

SURGERY IS THE GOLD STANDARD

DEBULK WHEN POSSIBLE- Definite Survival Advantage

✓ Somatostatin analogs effective in controlling hormonal syndrome

✓ PROMID suggests octreotide LAR controls tumor growth in midgut carcinoids

✓ Confirmatory phase 3 RADIANT Trials have established the Efficacy of Everolimus in Advanced NETs

✓ Results of PRRT very promising
The Role of Interventional Radiology in the Treatment of NET

Jonathan Kessler, MD
Assistant Clinical Professor
Division of Interventional Radiology
City of Hope Comprehensive Cancer Center
Disclosures

• No relevant disclosures
Role of Interventional Radiology

• What role does IR play in the treatment of metastatic NET?
  – I don’t know
  – More than we are currently doing
Role of Interventional Radiology

• What role does IR play in the treatment of metastatic NET?
  – Review the evolving data for treatment of NET liver metastases
  – Justify expanding treatments to more patients with NET liver metastases
NET Metastases

- NET incidence 8/100,000
- Distant metastases 44-73% at diagnosis
  - Small bowel 80-90%
  - Pancreas 60-70%
- Liver tumor involvement strong prognostic indicator

Pavel et al ENETS Consensus Guidelines for the Management of Patients with Liver and Other Distant Metastases from Neuroendocrine Neoplasms. Neuroendocrinology 2012
## Indications

<table>
<thead>
<tr>
<th>Symptomatic or</th>
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</thead>
<tbody>
<tr>
<td>Clinically significant tumor burden or</td>
</tr>
<tr>
<td>Clinically significant progressive disease</td>
</tr>
</tbody>
</table>

## Treatment Options

- Consider octreotide or lanreotide and/or
- Everolimus or
- Sunitinib or
- Cytotoxic chemotherapy or
- Hepatic regional therapy or
- Cytoreductive surgery / ablative therapy
Metastatic NET ENETS
Metastatic NET ENETS

- Resection of primary
- No extrahepatic spread

A. Simple pattern of LMs G1/G2 (unilobar or limited)
  - Resection (minor or anatomical)
  - Surgery contraindicated
  - Ablation (RFA, LITT, TACE)

B. Complex pattern of LMs G1/G2 (bilobar)
  - One-step surgery: Major liver resection ± RFA
  - Two-step surgery: Minor resection ± RFA, RPVE, RPVL, Sequential major liver resection
  - TACE TAE

C. Diffuse LMs G1/G2
  - Or surgery contraindicated
  - Small intestinal
    - SSA (IFN)
    - PRRT
  - Pancreatic
    - SSA (IFN)
    - Chemotherapy
    - Everolimus
    - Sunitinib
    - PRRT

- Selected cases (<1%)
- Liver transplantation
What are we doing?

N=824

- Supportive Care: 5%
- Chemotherapy: 17%
- Resection of Primary Tumor: 20%
- Liver Resection: 27%
- Surgical Resection + Transarterial Therapy: 15%
- Transarterial Therapy: 15%
Transarterial Therapy for Liver Metastases

- Stomach: 12.5%
- Pancreas: 17.8%
- Midgut: 10.7%
- Colorectal: 16.5%
- Unknown: 20.0%
Transarterial Therapy + Surgery

Overall Survival in Patients Treated Surgically

Log-rank p < 0.0001

- Liver resection
- Transarterial Therapy + Surgery
- Primary Tumor Resection
NET Metastases 5 yr Survival

Pavel et al. ENETS Consensus Guidelines for the Management of Patients with Liver and Other Distant Metastases from Neuroendocrine Neoplasms. Neuroendocrinology 2012
IR Treatments of Metastatic NET

• Who
  – Patient selection

• When
  – Indications and timing of therapy

• What
  – TACE vs TAE vs Y90
Limited Metastatic Disease
Percutaneous Ablation

• Resection vs Ablation
  – Lesions < 3 cm
    • No difference in survival or recurrence free survival
    • Procedure time, length of stay and blood loss were all lower in ablation group

Chen Ann Surg 2006; 243:321–328
Percutaneous Ablation

- Percutaneous Liver Ablation Guidelines
  - ≤ 3 lesions
  - ≤ 3 cm in size
  - Location amenable to ablation
  - No ablation modality proven to be better
    - RFA/Microwave/Cryo...
Percutaneous Ablation

• Percutaneous Liver Ablation Guidelines
  – ≤ 3 lesions 5 lesions
  – ≤ 3 cm in size 5 cm in size
  – Location amenable to ablation
  – No ablation modality proven to be better
    • RFA/Microwave/Cryo...
Limited Metastatic Disease
Limited Metastatic Disease
Extensive Metastatic Disease
Therapy Options

• Chamberlain et al
  - No difference in pain or hormonal symptom relief with either surgery or embolization when not with curative intent

Chamberlain et al. JCAS 2000 Apr; 190
Therapy Options

- Mayo et al
  - Retrospective IAT vs Surgery
    - 753 pts at 9 centers
      - Extrahepatic disease
        » 40.6% vs 16.2%
      - >50% liver involvement
        » 65% vs 26%
    - No difference in survival for asymptomatic pts with >25% tumor burden

Mayo et al Annals of Surg Onc 2011
Who Should Get Transarterial Therapy

• Unresectable or Recurrent disease
  – Symptom control
  – Limit progression

• Technically Resectable
  – Asymptomatic, non-bulky disease?
  – Extrahepatic disease?
When Should Patients Get LDT

• Early/Time of Diagnosis
  – RCT alpha interferon +/- embolization at time of diagnosis
    • No embo: 38% RR, 40% OS at 5yr
    • Embo: 60% RR, 75% OS at 5yr

• Late
  – Retrospective review 123 pts treated with embolization
    • Range of duration of liver disease 1-144 months
    • 80% overall RR
    • Duration of disease had no effect on RR, OS, PFS

Repeat Treatment

Sward et al

- 107 pts with midgut carcinoid
  - 1-4 treatments
- Median survival from tx 56 months

Arterial Therapies

• Bland embolization

• Chemoembolization

• Radioembolization
Transarterial Therapy
Transarterial Therapy
Transarterial Therapy
Transarterial Therapy
Does Regional Chemotherapy Add Benefit?

• TAE
  – Bland regimen
    • Gelfoam
    • PVA particles
    • Cyanoacrylate glue
    • Tris acryl gelatin microspheres
      – 40-700 micron

• TACE
  – Chemo regimen
    • cisplatin, vinblastine
    • Streptozocin, 5-fu
    • Streptozocin
    • Doxorubicin
    • Cisplatin, doxorubicin, mitomycin

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Method</th>
<th>Response %</th>
<th>Survival (months)</th>
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<tr>
<td>Dong et al</td>
<td>123</td>
<td>TACE</td>
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<td>De Baere et al</td>
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<td>67</td>
<td>TAE/TACE</td>
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<td>Gupta et al</td>
<td>49</td>
<td>TAE/TACE</td>
<td>TAE: 12% TACE 20%</td>
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<td>Maire et al *</td>
<td>26</td>
<td>TAE/TACE</td>
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• DEB vs cTACE in HCC
  (PRECISION V Trial)
  – Reduced liver toxicity and side effects
    • SAE: 30.6% vs 20.4%
    • Alopecia: 19.4% vs 2.2%
    • Max transaminase change 50% less

DEB- TACE

- Drug eluting bead TACE
  - Phase II 13 pts treated with doxorubicin beads
  - ORR 78%
  - 54% biloma formation
    - 4 required drainage
Radioembolization

• Yttrium 90
  – Pure beta-emitter with a half-life of 64.2 hours.
  – Tissue penetration of the emissions is 2.5 to 11 mm
  – Available in two forms Glass (HDE for HCC) and Resin (FDA for CRC)
  – Delivered via transarterial catheter and emits local high dose of radiation to tumor.
Yttrium 90 Microspheres

Pros
• Better short term tolerability
• Outpatient procedure
• Leave arteries patent for additional therapy

Cons
• Potential increased GI and pulmonary toxicity
• Cumulative hepatic radiation toxicity
Radioembolization

- Kennedy et al
  - Retrospective review 148 pts 10 centers
    - 67% small bowel
    - 19% pancreas
  - Grade 3/4 toxicity
    - Fatigue 6.5%
    - Nausea 3.2%
    - Pain 2.7%
    - Ascites 0.5%

Response Rate
CR - 2.7%
PR - 60.5%
SD - 22.7%
PD - 4.9%
## Radioembolization

<table>
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<th>Study</th>
<th>N</th>
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<td>Rhee et al</td>
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<td>Cao et al</td>
<td>58</td>
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<tr>
<td>Paprottka et al</td>
<td>42</td>
<td>55</td>
<td>NR (95% at 16 months)</td>
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<td>Memon et al</td>
<td>40</td>
<td>64% WHO 71% EASL</td>
<td>34</td>
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</tbody>
</table>
TACE vs TARE

• Pooled analysis of 37 articles with 1500 pts
  – TACE
    • ORR 58%
    • Median survival 35 months
  – TARE
    • ORR 63%
    • Median survival 28 months

• Conclusion
  – “Treatment strategies must be tailored individually for patients according to their disease, medical status, preference and quality of life considerations”

Yang et al Surgical Oncology 2012
What is the role of Interventional Radiology?

- Supportive Care: 5%
- Chemotherapy: 15%
- Resection of Primary Tumor: 17%
- Liver Resection: 27%
- Surgical Resection + Embolization: 16%
- Embolization: 21%
What is the role of Interventional Radiology?

- Liver Resection
- Ablation
- Embolization
- Primary Resection
- Chemotherapy
- Resection of Primary Tumor
- Liver Resection
- Surgical Resection + Embolization
- Embolization