The Role of Interventional Radiology in the Treatment of NET

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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>
<th>Clinically significant or</th>
<th>Clinically significant disease</th>
</tr>
</thead>
</table>

### Treatment Options

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

Morphological and functional imaging

Resection of primary

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

C. Diffuse LMs G1/G2
   - Or surgery contraindicated
   - Selected cases (<1%)
     - Small intestinal
       - SSA (IFN)
       - PRRT
       - Everolimus
     - Pancreatic
       - SSA (IFN)
       - Chemotherapy
       - Everolimus
       - Sunitinib
       - PRRT

No extrahepatic spread

Liver transplantation

TACE

TAE
What are we doing?

N = 824

Supportive Care
Chemotherapy
Resection of Primary Tumor
Liver Resection
Surgical Resection + Transarterial Therapy
Transarterial Therapy

California Cancer Registry 2005-2012
Treatments of Hepatic Metastases
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
Transarterial Therapy in Non-Surgical Patients

Overall Survival in Patients with Unresectable Disease

- Chemotherapy Alone
- Transarterial Therapy
- No Treatment

Log-rank $p = 0.0003$
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 vs. 5 lesions
  - ≤ 3 cm in size vs. 5 cm in size
  - Location amenable to ablation
  - No ablation modality proven to be better
    - RFA/Microwave/Cryo...
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
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
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 emb: 38% RR, 40% OS at 5yr
    - Emb: 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
- Chemoeembolization
- Radioembolization
Does regional chemotherapy add benefit?

- TAE
  - Bland regimen
    - Gelfoam
    - PVA particles
    - Cyanoacrylate glue
    - Tris acryl gelatin microspheres
      - 40–700 micron
  
- TACE
  - Chemotherapy
    - 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>
</tr>
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<tbody>
<tr>
<td>Dong et al</td>
<td>123</td>
<td>TACE</td>
<td>62</td>
<td>39</td>
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<tr>
<td>De Baere et al</td>
<td>20</td>
<td>TACE</td>
<td>80</td>
<td>NR</td>
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<tr>
<td>Vogel et al</td>
<td>48</td>
<td>TACEm / TACEgm</td>
<td>11/23</td>
<td>38 / 57</td>
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<tr>
<td>Loewe et al</td>
<td>23</td>
<td>TAE</td>
<td>73</td>
<td>69</td>
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<tr>
<td>Eriksson et al</td>
<td>41</td>
<td>TAE</td>
<td>50</td>
<td>80</td>
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</table>
## TACE/TAE

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Method</th>
<th>Toxicity</th>
<th>Response %</th>
<th>Survival (months)</th>
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<tbody>
<tr>
<td>Pitt et al</td>
<td>100</td>
<td>TAE/ TACE</td>
<td>TAE: 6.6</td>
<td>NR</td>
<td>25.5 / 25.7 NS</td>
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<tr>
<td></td>
<td></td>
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<td>TACE: 2.4 NS</td>
<td></td>
<td></td>
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<tr>
<td>Ruutianien et</td>
<td>67</td>
<td>TAE/ TACE</td>
<td>TAE: 22 %</td>
<td>38 / 22</td>
<td>39 / 44 NS</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>TACE: 25 %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gupta et al</td>
<td>49</td>
<td>TAE/ TACE</td>
<td>TAE: 12 %</td>
<td>25 / 50</td>
<td>Carcinoid: pNET: 18 / 33 *</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>TACE 20 %</td>
<td></td>
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<tr>
<td>Maire et al *</td>
<td>26</td>
<td>TAE/ TACE</td>
<td>TACE: 3 TAE: 2</td>
<td>92 / 100</td>
<td>2 yr: 100% / 80% NS</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

Bhagat et al CVIR 2013
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%

Kennedy et al Am J Clin Onc June 2008
### Radioembolization

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Response</th>
<th>Survival (median months)</th>
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<tbody>
<tr>
<td>Rhee et al</td>
<td>42</td>
<td>50</td>
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<td>Kennedy et al</td>
<td>148</td>
<td>63</td>
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<td>King et al</td>
<td>58</td>
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<td>Saxena et al</td>
<td>48</td>
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<tr>
<td>Cao et al</td>
<td>58</td>
<td>39</td>
<td>36</td>
</tr>
<tr>
<td>Paprottka et al</td>
<td>42</td>
<td>55</td>
<td>NR (95% at 16)</td>
</tr>
<tr>
<td>Memon et al</td>
<td>40</td>
<td>64% WHO 71% EASL</td>
<td>34</td>
</tr>
</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: 27%
- Chemotherapy: 15%
- Resection of Primary Tumor: 17%
- Liver Resection: 20%
- Surgical Resection + Embolization: 15%
- Embolization: 5%
What is the role of Interventional Radiology?

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