Interventional Oncology

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Trans-arterial Liver-directed Therapies for Metastatic NET

List of Interventional Oncology procedures
- Hepatic artery chemoembolization (TACE)
- Hepatic artery embolization (TAE)
- Hepatic artery radioembolization (SIRT)
- Portal vein embolization (PVE)
- Percutaneous thermal ablation:
  - RF and Microwave
- Cryoablation: Freezing tumors
- Chemical Ablation (PAE): absolute Ethanol

Octreotide
- Binds ssrt-2,3,5
- Relieves syndrome in 90%
- Decreases tumor markers
- Role in tumor stabilization
- Improved Progression Free Survival
  - 14.3 months vs 6 (p=0.00007)
  - PROMID study
**PROMID Study**

- Phase III placebo controlled multicenter trial in Germany
- 85 patients over 7 years (2001 – 2008)
- WDNEC (Ki-67 <2%)
- 75% had tumor liver burden <10%
- 38% had carcinoid syndrome
- Median 4.3 months from dx to enrollment
- Improved PFS for Octreotide
  - 14.3 months vs 6 (p=0.00007)

*Rinke et al, JCO 2009*

**When to Intervene?**

- Uncontrolled Symptoms
- Deterioration in Liver Function
- Increased Tumor Burden

**Patient Selection**

- Multidisciplinary Bi-weekly Conference
  - med onc, surg onc and IR
- Emphasis on curative therapies
  - Resection, Ablation
- TACE when not eligible for curative therapy

**How to Treat?**

<table>
<thead>
<tr>
<th>Center</th>
<th>Type</th>
<th>Treatment</th>
<th>Response (RECIST)</th>
<th>TTP (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>M.D. Anderson</td>
<td>GI NET</td>
<td>TAE/TACE</td>
<td>24%</td>
<td>22.7</td>
</tr>
<tr>
<td>Univ. Pennsylvania</td>
<td>NET</td>
<td>TAE</td>
<td>n/a</td>
<td>10</td>
</tr>
<tr>
<td>Univ. Pennsylvania</td>
<td>NET</td>
<td>TACE</td>
<td>n/a</td>
<td>55</td>
</tr>
<tr>
<td>Washington University</td>
<td>GI NET</td>
<td>TAE/TACE</td>
<td>32%</td>
<td>20</td>
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<tr>
<td>Institut Gustave Roussy</td>
<td>GI NET</td>
<td>DEB-TACE</td>
<td>80%</td>
<td>15</td>
</tr>
<tr>
<td>Multi-center</td>
<td>GI NET</td>
<td>Y90</td>
<td>43%</td>
<td>22-28 MS</td>
</tr>
</tbody>
</table>

*Gauer et al; Cardiovasc Intervent Radiol (2011) 34:566-572*
Why Bland Embolization?

- M.D. Anderson 2005, (n=123)
- GI Carcinoid (n=69)
  - No difference in response rate / survival
- Islet Cell Carcinomas (n=54)
  - Response rate (TACE 50% vs TAE 25%) ns
  - Prolonged survival (TACE 31 vs TAE 18 months) ns

(Gupta et al; Cancer 2005)

LC Bead Product

- 2 ml of LC Bead in saline
- 70 μm-150 μm, 100 μm-300 μm, 300 μm-500 μm and 700 μm-900 μm

Why Chemoembolization?

- U Penn: JVIR 2007, (n=67)
- No Difference in Severe Toxicities
  - TACE: 11/44 (25%)
  - Bland: 5/23 (22%)
  - 95% CI 0.4-4.0
- No difference in length of stay

(Ruutlainen: J Vasc Interv Radiol 2007)
**Why Chemoembolization?**

- 12 months Progression: TACE 0%, TAE 49%
- 3 Years: TACE: 35% were progression-free
- Symptom Control: Better with TACE
  - 15 months vs. 12 months (ns)
- Better Survival with TACE
  - 76% vs 68% at 2 years (ns)

(Ruutiala: J Vasc Interv Radiol 2007)

**TACE: CAM**

- Cisplatin 50 mg
  - No longer manufactured
- Adriamycin 30 mg
- Mitomycin 20 mg
- Ethiodol: 10 ml
- Volume: 20 ml

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**Hepatic Artery Chemoembolization in 122 Patients with Metastatic Carcinoid Tumor: Lessons Learned**

Mark Blamey - Osama AlSaif - Doru KhorosHZ
Joseph J. Phamco - Edward H. Martin - Bryan Palmer -
Lesley Gay - Brunon Khabbi -
F. Christopher Elisse - Manuela H. Shal

- Retrospective review of 122 patients
  - 1992 – 2004
- All patients considered “inoperable”
- Indications:
  - Liver tumor progression
  - Poorly controlled symptoms
  - Large tumor burden in liver

J Gastrointest Surg 2007;11:264-71

**Liver Directed Therapy at OSU**

- Lobar TACE
- Same Day Admit
- Octreotide Drip
TACE – OSU Experience

- Whole liver initially favored (75%)
  - Rarely done since 2004
- Complications 23%
- Mortality 5%
- Radiographic response = 82%
  - Median TTP = 19 months
- Biochemical response = 80%
  - Median TTP = 7 months
- Symptom response = 92%
  - Median TTP = 13 months

J Gastrointest Surg 2007;11:264-71

Predictors of Complications

- Tumor Burden > 70% (p=0.029)
- Bilioenteric anastomosis: Odds Ratio of liver abscess for TACE x67
- Whole Liver TACE vs. Partial (p=0.001)

J Roche & T de Baere; Europ Radiol 2003

Complications: The European Experience

- Major: 5.9% of Procedures
  - Transient hepatic or renal failure
  - Liver abscess
- Death: 1.6% Procedures
  - Liver + renal failure
  - Septicemia

A Roche & T de Baere; Europ Radiol: 2003

Contraindications

- Mostly Relative
- Hepatic Failure
  - Secondary to large tumor burden
- Portal Vein Thrombosis
  - Rare in NET patients
- Bilioenteric anastomosis
  - Abscess
Causes of Failure

- Poorly Vascularized Metastases
- Failure of TACE or failure to TACE?
- Failure in the dome:
  - Phrenic artery?
- Failure in the left lobe:
  - Left hepatic artery variant
- Intercostal Arteries

Unresponsive Lesions

Post-embolization changes

<table>
<thead>
<tr>
<th>Fresh</th>
<th>Repeat</th>
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</table>

Non-hepatic Arterial Supply

| Hepatic Artery | Phrenic Artery |
Non-hepatic Arterial Supply

Hepatic Artery

Phrenic Artery

Progression After TACE

- Maximum response at up to 18 months
- Year 1-3: New lesions or progression of old lesions
- Threshold for re-treatment?
- Second line Therapy?

Repeat TACE

- Challenges of Re-embolization
- Success of re-TACE despite the appearance of the arteries, yet ultimately limited by the arteries
Second Line Therapy

- Repeat TACE - if good first response
- Switch to Y-90 if early failure?
- Increase Sandostatin
- Nuclear Therapy

Drug-Eluting Beads

- Biocompatible PVA hydrogel bead which can be loaded with chemotherapy
  - Doxorubicin: DEBDOX
  - Irinotecan: DEBIRI
- Combines chemotherapy and embolization
- Early experience

DC Bead Before and After Loading with Doxorubicin

DC Bead Loading

- Negatively charged sulfonate interacts with positively charged doxorubicin hydrochloride or irinotecan hydrochloride
  - DC Bead Doxorubicin (DEBDOX)
  - DC Bead Irinotecan (DEBIRI)
DEB TACE

<table>
<thead>
<tr>
<th>Year</th>
<th>Author</th>
<th>N</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>2008</td>
<td>de Baere et al</td>
<td>20</td>
<td>PFS 15m</td>
</tr>
<tr>
<td>2011</td>
<td>Whitney et al</td>
<td>28</td>
<td>PFS 18m, OS 25m</td>
</tr>
<tr>
<td>2011</td>
<td>Gaur et al</td>
<td>18</td>
<td>PFS 14m</td>
</tr>
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Potential advantages of traditional TACE:
• Consistent delivery
• Ease of use
• Ability to evaluate response
• ???Cost (Disadvantage?)

Yttrium-90 Microspheres

• Radiolabelled particles
  – TheraSpheres® - MDS Nordion (HCC)
  – SIRSpheres – SIRTex (CRC)
• Embolized into hepatic artery
• High dose radiation to tumor
• Low dose radiation to liver
• β particle emission
  – 2-3mm of penetration

DEB TACE

• Evidence not as mature as with conventional TACE
• Ongoing Trials
• Higher than expected Toxicity
  – Potential role: for selective treatment?
• No evidence or justification for Irinotecan
Microspheres

Y-90 Results

- Kennedy: 148 patients, multiple centers
- 67% - No Toxicity (surprising)
- CR 3%, PR 60%, SD 23%, PD 5%
- High disease control - 95% control, mean survival 70 months
- Outpatient Process

Y-90 Process

- Outpatient treatment
- Angiographic Evaluation
  - presence of GI collaterals and lung shunting
- Y-90 Dose calculation and ordering:
  - 10 day delivery
- Actual treatment
- 4-6 weeks from referral to treatment

“Video used with permission from Nordion (Canada) Inc.”
Ongoing Questions

- Is TACE superior to TAE?
- DEB-TACE for selective treatment?
- Y90: promising
- Role of Intra-arterial therapies early in the course of the disease
- RCT difficult due to small population size, heterogeneity

Ohio State University NET Program

Endocrinologists
Lawrence Kirschner
Medical Oncologists
Manisha Shah
Rich Goldberg
Tanios Bekaii-Saab
Interventional Oncologists
Hooman Khabiri
Gregory Guy
Ali Rikabi
Jamal Al Taani
Surgical Oncologists
Mark Bloomston
Carl Schmidt
Sherif Mesrihelidin
Christopher Ellison
Clinic Team
Linda Vaders
Amber Thompson
Chad Galbraith
Dori Klemanski
Gail Davidson
Pathologists
Wendy Frankel
Paul Wakely
Clinical Trials Office
Minden Collamore
Katie Warden
Geneticists
Albert de la chapelle
Patients & Families
Radiation Oncologists
### Current Status of Vena Cava Filters in the Emerging Era of Retrievable Filters

<table>
<thead>
<tr>
<th>Gregory E. Guy, M.D.</th>
<th>Assistant Professor of Radiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retrievable Filters</td>
<td>Section of Interventional Radiology</td>
</tr>
<tr>
<td>The Ohio State University College of Medicine</td>
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</tr>
</tbody>
</table>

### VENOUS/IVC INTERRUPTION

#### MECHANICAL PREVENTION OF VTE

- Femoral vein ligation (late 1800s-1900s)
- IVC ligation (early-mid 1900s)
- Vena cava compartmentalization (mid-1900s)- sutures, clips, etc
- Vena cava filters (1960s-now)

### OUTLINE

- Brief history of venous/IVC interruption
- Evolution of vena cava filters
- Expanding list of indications for filter placement
- Growing number of vena cava filters placed annually
- Introduction of retrievable vena cava filters

### MECHANICAL PREVENTION OF VTE

#### REASONS FOR FAILURE

- Contralateral disease
- Collateral vein formation
- Surface thrombus
### MECHANICAL PREVENTION OF VTE

#### REASONS FOR FAILURE

- Operative morbidity and mortality
- Venous stasis
- Abrupt decrease in systemic venous return

### VENA CAVA FILTERS

#### CURRENT PERMANENT DEVICES

- Greenfield- steel 15 Fr.
- Greenfield- titanium 14.3 Fr.
- Bird’s nest 14 Fr.
- VenaTech 14.6 Fr.
- VenaTech LP 9 Fr.
- Simon nitinol 9 Fr.
- Trapease 8 Fr.

### MECHANICAL PREVENTION OF VTE

#### VENA CAVA FILTERS

- Greenfield vena cava filter (1973)
  percutaneous insertion 1984
  para-axial flow (intrinsic thrombolysis)
  over the wire delivery
  sheath 29.5 Fr OD

- Mobin-Uddin umbrella (1967)
  percutaneous insertion 1974
  unacceptable rates of IVC thrombosis
  elevated “downstream” pressure
  “upstream” surface thrombus
### Vena Cava Filters

#### Absolute Indications
- Contraindication to anticoagulation
- Complication of anticoagulation
- Failure of anticoagulation

#### Relative Indications
- Massive PE
- Iliofemoral thrombus
- Chronic or recurrent PE w/ PAHTN
- Patient non-compliance
- Unsteady gait or ataxia
- Venous thrombolysis
- Primary (spinal cord injury, multi-trauma)
- Peri-operative (primary or secondary)

#### Summary of Trends
- Lower profile delivery systems
- Expanding indications

#### NHRS database 1979-1999
- ~25x increase in annual VCF placements

#### Single institution study 1995-2005
- ~6x increase in annual VCF placements

#### Increase in transient indications
- Increase in primary prevention
- >50% multiple recent series
### Vena Cava Filters: Retrievable Filters

- US approval ~2003
- All approved for permanent use
- Low rates of PE and IVC thrombosis
- High retrieval rates
- No maximum dwell time to retrieve

### Retrievable Vena Cava Filters Assumptions

- Low procedural complication rate
- Effective
- Low/no long term complications
- Retrievable filters have similar performance to permanent filters

### Vena Cava Filters: Retrievable Filters

- Celect (Gunther tulip)
- G2 (Recovery)
- OptEase
- Option
- ALN

### Vena Cava Filters: Permanent Filters: Meta-Analysis

- Procedural complications 4-11%
- Recurrent PE 2-5%
- IVC thrombosis 0-28%
- IVC perforation 0-40%
- Tilting, migration, other

* good data lacking*
### VENA CAVA FILTERS
**PREPIC STUDY GROUP**
- NEJM, 1998
- Circulation, 2005
- Nearly 400 patients
- Randomized anticoagulation and IVC filter anticoagulation alone

### RETRIEVABLE FILTERS
- Approval data short term
- Retrieval rates as low as 10%
- Observations fracture migration perforation
  - “one device for all”
  - *good data lacking*

### VENA CAVA FILTERS
**PREPIC STUDY GROUP**
- Filter group reduction in PE (significant at 12 days) increase in DVT (significant)
- No difference in mortality
- No difference in post-thrombotic changes
- No difference in overall incidence of VTE

### RETRIEVABLE FILTERS
**OUTCOMES- REVIEW**
- Retrieval 34% (12-45%)
- PE 1.3% (0.7-4%)
- DVT 5.4% (0.8-14%)
- IVC stenosis/thrombosis 2.8% (0.6-8%)
RETRIEVABLE FILTERS
OUTCOMES- REVIEW

- Fracture
- Migration
- Perforation

- Most occurred >30 days after placement
RETRIEVABLE FILTERS

OUTCOMES

- Retrieval success inversely related to dwell times
- Reports of successful retrieval at long (years) dwell times

REASONS FOR NON-RETRIEVAL

- No intent to retrieve
- Lost to follow-up
- Patient refusal
- Death
- Lack of familiarity
## Retrievable Filters

### Reasons for Failure to Retrieve

- Trapped thrombus
- Incorporation into IVC wall (hook)
- Failure of strut collapse
- ?IVC perforation

### Proposed Algorithm for Retrieval

- Primary prevention (prophylactic)
- Secondary prevention (therapeutic)

### Retrievable Filters: Trapped Thrombus

- Controversy re: how much thrombus is "safe" to retrieve
- Options
  - retrieve vs initiate/continue anticoagulation
  - re-assess for retrieval
- Duration of anticoagulation unknown

### Algorithm - Primary

- Lower extremity venous duplex exam
- Bilateral iliac venograms
- IVC’gram
- Attempt retrieval
RETRIEVABLE FILTERS
ALGORITHM- SECONDARY

- Resume full anticoagulation
- IVC’gram
- Attempt retrieval
VENA CAVA FILTERS
SUMMARY OBSERVATIONS

• Vena cava filters are effective
• All filters may have complications
• The exact long term role of vena cava filters is unknown
• The long term performance of retrievable vena cava filters is evolving

RETRIEVABLE FILTERS
SUGGESTIONS

• More discriminate selection of filter type
• Better follow-up of filter patients
• Improve retrieval rates
  dedicated follow-up “service”
  automated note on DC instructions
  more widespread familiarity of devices