Liver-Directed Therapy for Primary and Metastatic Hepatic Malignancies

L. Andrew DiFronzo MD  
Hepatobiliary and Oncologic Surgery  
Chief of Surgery, Kaiser Permanente Los Angeles

Overview

- Liver Directed Therapies
- Hepatic Resection  
  - General Criteria for Resectability
- Metastatic Malignancies  
  - Colorectal
  - Neuroendocrine
  - Non-colorectal, non-neuroendocrine
- Primary Cancers  
  - HCC
  - Extra- and Intra-Hepatic Cholangiocarcinoma

Liver Directed Therapies

- Resection
- Ablation  
  - RFA
  - Cryoablation
  - Chemical
- Chemoembolization (TACE)
- Hepatic artery infusion
- Microwave ablation
- Selective Internal Radiation Therapy (SIRT)
Hepatic Resection

- Mortality < 5%
  - Zero mortality in many series
- Hemorrhage control and reduction in need for transfusion
  - Low CVP anesthesia
  - Novel methods of parenchymal transection
  - Hemodilution
- Liver dysfunction and failure

Radiofrequency Ablation

- High-frequency alternating current creates heat that destroys tumor cells
- Operative (open or laparoscopic) or percutaneous approach
- Spares hepatic parenchyma

RFA Benefits and Limitations

- Less invasive
- Fewer complications
- Decreased expense
- Simultaneous treatment with systemic therapies
- Does not preclude subsequent resection
- Size limitation
- “Heat sink” effect
- Adjacent organs may require open approach
Transarterial Chemoembolization (TACE)

- Relies on hepatic artery as primary blood supply for tumor
- Directed chemotherapy followed by embolization of tumor's arterial blood supply
- Minimally invasive
- Safe
- Can be repeated

Chemical Ablation

- Only HCC in cirrhotic livers
  - Soft tumor with hard surrounding liver allows diffusion into tumor only
- Ethanol ablation most common
  - PEI (percutaneous ethanol ablation)
- Acetic acid also used
- Safe and minimally invasive
- Multiple treatments needed

Hepatic Artery Infusion

- Metastases derive most blood from hepatic artery
- Improved progression-free survival in liver in pts with hepatic resection
  - No overall survival benefit
- Enthusiasm waned w/ modern systemic therapy
- NSABP C-09
  - CAPOX with or without HAI in resected pts
- Now what?
Hepatic Resection
General Criteria for Resectability

- Preservation of functional hepatic parenchyma
  - Preservation of two contiguous liver segments
  - Normal liver: 25% liver remnant
  - Cirrhotic liver 50-75% depending on Child class
- Operative risk
- Ability to obtain a negative margin
  - R0 resection
- Good performance status
  - ECOG 0-1

Resection (and Other Liver-Directed Therapy) for Metastatic Disease
Prognostic Indicators and Surrogates for Tumor Biology

- Disease-free interval
  - >12 months better prognosis
- Number of metastases
- Number of organs
  - 1 vs greater than one
- Site of metastases
  - Visceral vs non-visceral
- Response to systemic therapy

Which of the following patients is a good candidate for hepatic resection for metastatic disease?

a) 45 y/o M w/ metastatic melanoma to bilateral lungs and liver
b) 88 y/o F w/ severe COPD requiring home O2 w/ a single liver metastasis from colon ca resected 5 yrs ago
c) 56 y/o F w/ synchronous primary breast cancer and a single liver metastasis
d) 70 y/o M w/ 10 liver metastases and multiple nodal metastases from neuroendocrine carcinoma
e) 60 y/o F w/ 2 liver metastases from colon cancer treated 3 years ago, s/p systemic therapy w/ a good radiographic response
Colorectal Liver Metastases

“Hepatic resection for metastases from colorectal cancer is of dubious value”
Silen, 1989

- Standard of care
- Increasingly offered to patients
- ~10,000-15,000 patients are candidates for curative resection yearly
  - 5-yr survival of 30-40%
  - around 4000 pts/year have long-term survival

Hepatic Resection
Classic Contraindications

- 4 or more lesions
- Bilobar disease
- Extrahepatic disease
- Synchronous metastases
- Surgical margin <1 cm
- Inadequate remnant liver
- Portal lymph node involvement

Hepatic Resection for CRC Mets
Current Contraindications

NONE
(well...sort of)
Hepatic Resection for CRC Mets
Current Absolute Contraindications

- Unresectable extrahepatic disease
- Inadequate remnant liver (despite staged resection, PVE)
  - Over 70% of liver, or 6 segments
- Inability to obtain R0 resection (?)

No Prospective Randomized Trial Exists

- In retrospective series, resected patients have survival significantly better than all other groups
  - Patients with resectable disease who do NOT undergo resection have median survival 12 months shorter than resected patients
  - 16% 10-yr survival; actual 20 year survivors

Scheele, Br J Surg 1990

“Trends in Long-Term Survival Following Liver Resection for Hepatic Colorectal Metastases”
Choti et al, Ann Surg 2002

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<td>Overall Survival (%)</td>
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<td>3-Yr</td>
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<td>5-Yr</td>
<td>31</td>
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<td>Median Survival (mo)</td>
<td>36</td>
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“Survival After Hepatic Resection for Colorectal Metastases: A 10-Year Experience”
Wei et al, Ann Surg Oncol 2006

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<td>47</td>
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<td>10-Yr</td>
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<td>Disease-Free Survival (%)</td>
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<td>5-Yr</td>
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<td>27</td>
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<tr>
<td>10-Yr</td>
<td>na</td>
<td>22</td>
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</table>

Increasing Application (and Success) of Hepatic Resection

- Better patient selection
  - Advances in imaging
  - Response to chemotherapy
- Improved operative safety
- Use of innovative modalities
  - Neoadjuvant chemotherapy
  - Portal vein embolization
  - Local ablative therapies
  - Staged resection

“Clinical Score for Predicting Recurrence After Hepatic Resection for Metastatic Colorectal Cancer”
Fong et al, Ann Surg 1999

- 1001 consecutive cases
- 13 years, single institution
- 5-yr survival 37%
- 10-yr survival 22%
- Clinical Risk Score (CRS) devised to assist selection of pts for resection
### Predictors of Recurrence: Factors Useful in Risk Score

<table>
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<tr>
<th>Predictors</th>
<th>Hazard</th>
<th>Coefficient</th>
<th>p value</th>
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<td>Positive Margin</td>
<td>1.7</td>
<td>0.5</td>
<td>0.004</td>
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<td>Extrahepatic Disease</td>
<td>1.7</td>
<td>0.5</td>
<td>0.003</td>
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<tr>
<td>&gt; 1 Tumor</td>
<td>1.5</td>
<td>0.4</td>
<td>0.0004</td>
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<td>CEA &gt; 200ng/mL</td>
<td>1.5</td>
<td>0.4</td>
<td>0.01</td>
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<tr>
<td>Size &gt; 5 cm</td>
<td>1.4</td>
<td>0.3</td>
<td>0.01</td>
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<td>Node (+) Primary</td>
<td>1.3</td>
<td>0.28</td>
<td>0.02</td>
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<td>DFI &lt; 12 months</td>
<td>1.3</td>
<td>0.25</td>
<td>0.03</td>
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<tr>
<td>Bilateral Tumor</td>
<td>0.9</td>
<td>--</td>
<td>0.4</td>
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*Fong et al, Ann Surg 1999*

### Clinical Risk Score for Tumor Recurrence

<table>
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<tr>
<th>Score</th>
<th>Survival (%)</th>
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<tr>
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<td>2-yr</td>
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<tr>
<td>0</td>
<td>79</td>
</tr>
<tr>
<td>1</td>
<td>76</td>
</tr>
<tr>
<td>2</td>
<td>73</td>
</tr>
<tr>
<td>3</td>
<td>67</td>
</tr>
<tr>
<td>4</td>
<td>45</td>
</tr>
<tr>
<td>5</td>
<td>45</td>
</tr>
</tbody>
</table>

*Fong et al, Ann Surg 1999*

### Case 1

72 y/o woman s/p partial colectomy 8 yrs ago. T3N0. CEA =124. There is a single 7 cm metastasis.
Case 1
What is this patient’s Clinical Risk Score?

a) 0  
b) 1  
c) 2  
d) 3  
e) 4

Case 1
What therapy would you recommend?

a) Hepatic resection  
b) Hospice  
c) Systemic therapy only  
d) RFA  
e) Hepatic artery infusion and systemic therapy

Case 1 Follow-Up

<table>
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<th>Hepatic resection</th>
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<tr>
<td><img src="image" alt="Diagram" /></td>
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<tr>
<td>NED for 1 year</td>
</tr>
<tr>
<td>Recurred in liver, lung</td>
</tr>
<tr>
<td>Survived 2 years after diagnosis of recurrent tumor, receiving systemic therapy</td>
</tr>
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</table>
What Happened?

- Two main possibilities:
  - CRS not reliable in a different institution
  - No prognostic criteria are definitive enough to exclude a curative resection (and vice versa)

Are Risk Scoring Systems Reliable and Valuable?

- 662 pts w colorectal liver mets treated at Mayo clinic from 1960-1995
- Applied 3 different scoring systems to Mayo cohort to validate the models
- Conclusion: models only marginally better than chance in predicting recurrence and survival

"Actual 10-Year Survival After Resection of Colorectal Liver Metastases Defines Cure"

- 612 pts with 10 yr follow-up
- 102 (17%) actual 10 yr survivors
- 1/3 died of recurrent disease after 5 yrs


Fong CRS applied to Mayo cohort

Tomlinson et al, J Clin Oncol 2007

Overall survival by CRS
Case 2
66 y/o woman s/p transverse colectomy 1 year ago.
T3N0
CEA =2000.

Case 2
The best therapy at this time is:
a) Immediate hepatic resection
b) TACE and systemic therapy
c) Systemic therapy then possible resection
d) Resection w/ RFA, hepatic artery infusion
e) Total hepatectomy and orthotopic liver transplantation

After Pre-Op Systemic Therapy

Case 1
Pt underwent left hepatectomy
Path showed 2.5 cm metastatic adenocarcinoma w/ 2 subcentimeter satellites, margins neg
"Resection of Nonresectable Liver Metastases from Colorectal Cancer After Neoadjuvant Chemotherapy"

434 pts w/ Colorectal Metastases

104 pts (24%) initially resectable
330 pts (76%) initially unresectable

Chronomodulated 5-FU and oxaliplatin chemo

277 pts (84%) remained unresectable
63 pts (16%) underwent liver resection

Neoadjuvant Chemotherapy

- 40% 5-yr overall survival
- 34 pts (66%) recurred in liver at mean of 42 mo - Repeat hepatectomy performed in 15 (44%)
- 25 pts (47%) w/ extrahepatic recurrence
- 93 resections inc. liver, lung, abdominal

"Tumor Progression While on Chemotherapy: Contraindication to Liver Resection for Multiple Metastases?"
Adam et al, Ann Surg 2004

101 pts w/ ≥ 4 Metastases
Pre-Op Chemo

Response 56 pts (44%)
Stable Disease 39 pts (30%)
Progression 34 pts (34%)

131 pts Liver Resection
Tumor Progression on Chemo

- 28% 5-yr overall survival
- 37% 5-yr overall survival for patients with response to preop chemo
- Disease control before surgery crucial to prolonged survival

Adam et al, Ann Surg 2004

Pre-Op Systemic Therapy Questions

- Indications
- Optimal timing of surgery
  - Complete response or just enough to render resectable?
  - Borderline resectability—resect 1st?
- Ability to accurately determine response
- CASH (Chemotherapy-Associated Steatohepatitis)
  - Fatty infiltration → fibrosis → frank cirrhosis
- Costs
  - 6 mo course of treatment: $180,000

Should All Lesions Be Resected After Pre-Op Systemic Therapy?

- Remnants of uncertain malignant potential (RUMP)
  - Only 3/22 pts (14%) had pathologic CR
  - Median 20% viable neoplasm (range 0-60%) recovered per lesion

Znajda et al, J Gastrointest Surg 2006

- “Missing” liver metastases
  - 15 pts undergoing hepatic resection after chemo
  - 11 “missing” mets @ exploration
  - Only 27% recurrence at 31 months after radiologic CR

Elias et al, J Surg Oncol 2004
Complete Pathologic Response After Pre-Op Chemo

- 767 pts underwent pre-op chemo between 1985-2006
- 29 (4%) w/ complete PR
  - Improved 5 and 10-yr survival
- No relationship to pts who had a complete CR

Adam et al, J Clin Oncol 2008

Case 3
64 y/o woman who presented w/ abdominal pain and bloating in 1/06.
CT showed multiple liver mets.
CEA =3900.
Primary cancer identified as rectum. Asymptomatic.

The best therapy at this time is:

- a) Immediate synchronous hepatic and colon resection
- b) Systemic therapy then synchronous hepatic and colon resection
- c) Hepatic artery infusion and systemic therapy
- d) Systemic therapy then staged hepatic and colon resection using portal vein embolization
- e) Systemic therapy and TACE
Case 3 Follow-Up

- Underwent systemic therapy
  - FOLFOX + bevacizumab
- Proctectomy w/ multiple wedge resections of left hemiliver mets on 1/07
- Additional systemic therapy
- Portal vein embolization 4/07
- 2nd stage hepatectomy 5/07

Portal Vein Embolization

- Obstruct portal venous flow to side of liver ipsilateral to lesion
- Induce contralateral hypertrophy
- Increase size of future liver remnant
“Preoperative Portal Vein Embolization for Extended Hepatectomy”

Hemming et al, Ann Surg 2003

<table>
<thead>
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<th>PVE Group (n=31)</th>
<th>Non-PVE Group (n=21)</th>
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<tr>
<td>Gender M:F</td>
<td>19:12</td>
<td>13:8</td>
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<tr>
<td>Age (range)</td>
<td>61 (31-62)</td>
<td>59 (33-76)</td>
<td>NS</td>
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<tr>
<td>O.R. Time, min</td>
<td>285</td>
<td>270</td>
<td>NS</td>
</tr>
<tr>
<td>Blood Loss, mL</td>
<td>640</td>
<td>660</td>
<td>NS</td>
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<tr>
<td>Liver Failure</td>
<td>3 (10%)</td>
<td>7 (33%)</td>
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<tr>
<td>Peak Bilirubin</td>
<td>2.6 ± 1.2</td>
<td>5.0 ± 5.1</td>
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<tr>
<td>FFP Requirement</td>
<td>0.7 ± 1.4 u</td>
<td>2.9 ± 3.9 u</td>
<td>0.006</td>
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<tr>
<td>Length of Stay</td>
<td>8.7 ± 2.3 d</td>
<td>11.3 ± 5.7 d</td>
<td>0.03</td>
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</table>

Staged Resection

1st Stage Hepatectomy

2nd Stage Hepatectomy

PVE

Long Term Results of 2-Stage Hepatectomy

- 59 pts (out of 262) w/ initially unresectable mets who required two hepatectomies
  - Mean no. of mets 9
- 2-stage approach feasible in 41 of 59 patients (69%)
- 5-yr survival 31% by intention-to-treat

Wicherts et al, Ann Surg 2008
RFA vs. Resection
Colorectal Metastases

- 180 pts treated w/ resection vs RFA
  - Comparable w/ respect to primary tumor stage, nodal status, GPA, met size, CEA
- Higher local recurrence after RFA
  - 37 vs 5% at median 31 mo
- Worse overall and disease-free survival
  - 27 vs 71% overall 5-yr survival
  - 0 vs. 50% 5-yr DFS

Worse overall and disease-free survival

Aloia et al, Arch Surg 2006

RFA for Colorectal Metastases
Current Uses

- Patients with small lesions (<3 cm ideal) who are unresectable due to underlying liver disease
- Patients with intra-hepatic recurrence s/p hepatectomy, who are not candidates for repeat hepatectomy
  - Should be NED elsewhere

“...It is obvious that biological behaviour prevails over surgical enthusiasm in deciding the fate of patients with colorectal liver metastases”

Scheele, 1990
“In the world of Surgical Oncology
Biology is King
Selection is Queen
Technical maneuvers are the Prince and Princess

Occasionally the Prince or Princess tries to usurp the throne; they almost always fail to overcome the powerful forces of the King and Queen”

Cady, 1997

Neuroendocrine Metastases
• Can aggressive therapy prolong survival?
  – Generally indolent behavior
  – Extensive hepatic and extra-hepatic metastases
• Palliation of symptoms
• Multiple Treatment Options:
  – Resection +/- Ablative Therapies
  – TACE
  – Systemic Therapy

Case 4
55 y/o F s/p resection of a “pancreatic endocrine tumor” in 2004.
One large liver metastasis, two smaller ones.
Elevated gastrin, urinary 5-HIAA.
Progressed on Octreotide + IFN trial.
Case 4
The best approach now is:

a) Resection
b) TACE then resection
c) RFA
d) Liver transplantation
e) Hepatic artery infusion

Does hepatic resection improve survival in metastatic neuroendocrine tumors?

<table>
<thead>
<tr>
<th>Series</th>
<th>No. of Subjects</th>
<th>Treatment</th>
<th>3-Year Survival (%)</th>
<th>5-Year Survival (%)</th>
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<td>Musunuru 2006</td>
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<td>Medical</td>
<td>31</td>
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<td></td>
<td>18</td>
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<td></td>
<td>15</td>
<td>Surgery</td>
<td>92</td>
<td>73</td>
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TACE followed by Resection?

• Potential benefits:
  – May decrease tumor size, facilitate resection
    • Decrease release of vasoactive amines
  – Use in combination with resection and/or ablation to help cytoreduce tumor
• Limitations:
  – Tumor progression
"Neuroendocrine Hepatic Metastases: Does Aggressive Management Improve Survival?"

Touzios et al, Ann Surg 2005

<table>
<thead>
<tr>
<th>Resection/ Ablation</th>
<th>TACE +/- Resection/ Ablation</th>
<th>Non-Aggressive</th>
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<tbody>
<tr>
<td>Symptom Improvement (%)</td>
<td>95*</td>
<td>88*</td>
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<td>30-Day Mortality (%)</td>
<td>5.3</td>
<td>5.6</td>
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<tr>
<td>Survival</td>
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<tr>
<td>Median, mo</td>
<td>&gt;96*</td>
<td>50*</td>
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<tr>
<td>5 Yrs (%)</td>
<td>72*</td>
<td>50*</td>
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*p < 0.05 compared to Non-aggressive

Non-colorectal, Non-neuroendocrine Metastases
- Diverse group of malignancies
- Limited but growing body of data
- Patients w/ metastases from GU primaries have best survival
- Breast cancer best studied

Modern Series
Liver Resection for Non-Colorectal, Non-Neuroendocrine Metastasis

<table>
<thead>
<tr>
<th>Series</th>
<th>Number</th>
<th>5-Yr Survival (%)</th>
<th>Operative Mortality (%)</th>
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<tr>
<td>Harrison 1997</td>
<td>96</td>
<td>37</td>
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<td>Hemming 2000</td>
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<td>Laurent 2001</td>
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<td>Yamada 2001</td>
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<td>Takada 2001</td>
<td>14</td>
<td>NR</td>
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<td>Karavias 2002</td>
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<td>Weitz 2005</td>
<td>141</td>
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<td>Ercolani 2005</td>
<td>142</td>
<td>34</td>
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“Hepatic Resection for Noncolorectal Nonendocrine Liver Metastases: Analysis of 1452 Patients”
Adam et al, Ann Surg 2006

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Number</th>
<th>5-Yr Survival (%)</th>
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<td>Adrenal</td>
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<td>Breast</td>
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<td>Renal</td>
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<td>Stomach</td>
<td>64</td>
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<td>15</td>
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<tr>
<td>Ocular Melanoma</td>
<td>164</td>
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<tr>
<td>Pulmonary</td>
<td>32</td>
<td>8</td>
<td>16</td>
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</table>

Case 5
62 y/o F s/p mastectomy 14 yrs ago for node positive ER neg cancer. Received radiation and chemo. Elevated CA 2729 noted. Biopsy-proven ER + liver metastasis.

Select the most appropriate therapy:

a) Systemic therapy only
b) Systemic therapy followed by resection if good response
c) RFA and systemic therapy
d) Immediate hepatic resection
e) Hospice
Case 5 Follow-Up

- Started on Femara
- Excellent response
- Underwent segmental liver resection
  - Path: 3 cm metastatic carcinoma c/w breast primary, margin neg

“Is Liver Resection Justified for Patients With Hepatic Metastases From Breast Cancer?”
Adam et al, Ann Surg 2006

- 108 patients w/ breast cancer liver mets
  - 1984-2004
- Hepatic resection offered to all pts provided that:
  - Curative resection feasible
  - Extrahepatic disease controlled
- 84% received chemo between diagnosis and hepatic resection of liver mets
- Partial response to treatment in 78%
- 83% underwent post-resection systemic therapy

Liver Resection for Breast Cancer
Overall Survival

- Median follow-up 38 months
- Overall survival from hepatic resection:
  - Median 32 months
  - 5-yr survival 37%
- Overall survival from liver mets diagnosis:
  - Median 46 months
  - 5-yr survival 41%

Adam et al, Ann Surg 2006
Hepatic Resection for Breast Cancer Liver Metastases
Published Results (Modern Series, >10 Subjects)

<table>
<thead>
<tr>
<th>Series</th>
<th>No. of Subjects</th>
<th>Median Survival (mo)</th>
<th>5-Year Survival (%)</th>
<th>Mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selzner 2000</td>
<td>17</td>
<td>25</td>
<td>22</td>
<td>6</td>
</tr>
<tr>
<td>Yoshimoto 2000</td>
<td>25</td>
<td>34</td>
<td>NR</td>
<td>--</td>
</tr>
<tr>
<td>Pocard 2001</td>
<td>65</td>
<td>47</td>
<td>46</td>
<td>0</td>
</tr>
<tr>
<td>Carlini 2002</td>
<td>17</td>
<td>53</td>
<td>46</td>
<td>0</td>
</tr>
<tr>
<td>Vlastos 2004</td>
<td>31</td>
<td>63</td>
<td>61</td>
<td>0</td>
</tr>
<tr>
<td>Sakamoto 2005</td>
<td>34</td>
<td>36</td>
<td>21</td>
<td>0</td>
</tr>
<tr>
<td>d’Annibale 2005</td>
<td>18</td>
<td>32</td>
<td>30</td>
<td>0</td>
</tr>
<tr>
<td>Ercolani 2005</td>
<td>21</td>
<td>42</td>
<td>25</td>
<td>0</td>
</tr>
<tr>
<td>Adam 2006*</td>
<td>454</td>
<td>45</td>
<td>41</td>
<td>NR</td>
</tr>
</tbody>
</table>

Hepatic Resection for Breast Cancer
Prognostic Factors for Overall Survival

- Disease-free interval
  - DFI <12 months vs. > 12 months
    - 9 vs. 27 months  
      Selzner et al, Surgery 2000
  - DFI < 48 months vs. > 48 months
    - 55% vs. 86% 3-Yr Survival  
      Pocard et al, Ann Chir 2001
- Presence of extrahepatic metastases
  Sakamoto et al, World J Surg 2005
- Response to systemic therapy
  - 42% response vs 0% progression 5 yr survival
- Margin status
  Adam et al, Ann Surg 2006
  - 43% R0/R1 vs 10% R2 5-yr survival

Hepatocellular Carcinoma
Multiple Treatment Options

- Resection
- Total hepatectomy w/ orthotopic liver transplantation (OLT)
- Trans-arterial chemoembolization (TACE)
- Radiofrequency Ablation (RFA)
- Percutaneous ethanol injection (PEI)
- Systemic therapy
Hepatocellular Carcinoma
Hepatic Resection

- Historical “gold standard” but changing
- Significant limitation of preserving enough function hepatic parenchyma
  - Limits applicability in cirrhotic patients
- High morbidity
- Invasive

Hepatocellular Carcinoma
Hepatic Resection: Selected Series

<table>
<thead>
<tr>
<th>Series</th>
<th>Number</th>
<th>3-Yr Survival (%)</th>
<th>5-Yr Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Franco 1990</td>
<td>72</td>
<td>51</td>
<td>NR</td>
</tr>
<tr>
<td>Nagasue 1993</td>
<td>229</td>
<td>51</td>
<td>23</td>
</tr>
<tr>
<td>Llovet 1999</td>
<td>77</td>
<td>62</td>
<td>51</td>
</tr>
<tr>
<td>Zhou 2001</td>
<td>1000 (&lt;5cm)</td>
<td>77</td>
<td>65</td>
</tr>
<tr>
<td></td>
<td>1366 (≥5cm)</td>
<td>48</td>
<td>37</td>
</tr>
<tr>
<td>Ercolani 2003</td>
<td>224</td>
<td>63</td>
<td>43</td>
</tr>
<tr>
<td>Shimozawa 2004</td>
<td>135</td>
<td>73</td>
<td>55</td>
</tr>
</tbody>
</table>

Hepatocellular Carcinoma
Liver Transplantation

- Best outcomes
  - Improved chance for cure by obtaining wide margins and removing liver at risk for future tumor
  - Treats underlying liver disease and portal hypertension
    - Survival limited by cirrhosis and progressive liver failure
- Primary limitation is organ donor supply
Liver Transplantation For HCC
Best Reported Outcomes

<table>
<thead>
<tr>
<th>AUTHOR, JOURNAL, YR</th>
<th>CENTER</th>
<th>N</th>
<th>1-YR Survival (%)</th>
<th>5-YR Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mazzaferro, NEJM 1996</td>
<td>Milan, Italy</td>
<td>48</td>
<td>84%</td>
<td>74%</td>
</tr>
<tr>
<td>Llovet, Hepatology 1998</td>
<td>Barcelona, Spain</td>
<td>58</td>
<td>84%</td>
<td>74%</td>
</tr>
<tr>
<td>Bismuth, Sem Liver Dis 1999</td>
<td>Villejuif, France</td>
<td>45</td>
<td>82%</td>
<td>74%</td>
</tr>
<tr>
<td>Jonas, Hepatology 2001</td>
<td>Berlin, Germany</td>
<td>120</td>
<td>90%</td>
<td>71%</td>
</tr>
<tr>
<td>Yao, Hepatology 2001</td>
<td>San Francisco</td>
<td>64</td>
<td>87%</td>
<td>73%</td>
</tr>
</tbody>
</table>

Adapted from Bruix and Llovet, Hepatology 2002

RFA vs Other Ablative Therapies
Selected RCTs

<table>
<thead>
<tr>
<th>Series</th>
<th>No. of Subjects</th>
<th>Treatment</th>
<th>Treatments Per Tumor</th>
<th>Overall Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lin 2004</td>
<td>62</td>
<td>RFA</td>
<td>1.1</td>
<td>74% 5-Yr</td>
</tr>
<tr>
<td></td>
<td>50</td>
<td>PEI</td>
<td>5.4</td>
<td>53% 5-Yr</td>
</tr>
<tr>
<td>Shilina 2005</td>
<td>118</td>
<td>RFA</td>
<td>2.1</td>
<td>74% 4-Yr</td>
</tr>
<tr>
<td></td>
<td>114</td>
<td>PEI</td>
<td>6.4</td>
<td>57% 4-Yr</td>
</tr>
</tbody>
</table>

Adapted from Lau et al, Ann Surg 2009

RFA as Primary Treatment of Resectable HCC

- 180 pts w/ HCC ≤ 5 cm randomized to either percutaneous RFA or resection

<table>
<thead>
<tr>
<th>Overall Survival</th>
<th>Percutaneous RFA</th>
<th>Hepatic Resection</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Yr (%)</td>
<td>95.8</td>
<td>93.3</td>
<td>NS</td>
</tr>
<tr>
<td>4 Yrs (%)</td>
<td>67.9</td>
<td>64.0</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Disease Free Survival</th>
<th>Percutaneous RFA</th>
<th>Hepatic Resection</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Yr (%)</td>
<td>85.9</td>
<td>86.6</td>
<td>NS</td>
</tr>
<tr>
<td>4 Yrs (%)</td>
<td>46.4</td>
<td>51.6</td>
<td></td>
</tr>
</tbody>
</table>

Chen et al, Ann Surg 2006
### RFA as Primary Treatment of Unresectable HCC

- No randomized trials, only retrospective cohort studies

<table>
<thead>
<tr>
<th>Series</th>
<th>No. of Subjects</th>
<th>Mortality/ Morbidity (%)</th>
<th>5-Year Survival (%)</th>
<th>Tumor size, cm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buscarini 2001</td>
<td>88</td>
<td>0/2.3</td>
<td>33</td>
<td>&lt;3.5</td>
</tr>
<tr>
<td>Lencioni 2005</td>
<td>187</td>
<td>0/2</td>
<td>48</td>
<td>2.8</td>
</tr>
<tr>
<td>Raut 2005</td>
<td>194</td>
<td>1/12</td>
<td>55</td>
<td>3.3</td>
</tr>
<tr>
<td>Machi 2005</td>
<td>65</td>
<td>1.2/4.8</td>
<td>40</td>
<td>3.2</td>
</tr>
<tr>
<td>Tateishi 2005</td>
<td>319</td>
<td>0/4</td>
<td>54</td>
<td>2.6</td>
</tr>
<tr>
<td>Cabassa 2006</td>
<td>59</td>
<td>0/1.7</td>
<td>43</td>
<td>3.1</td>
</tr>
<tr>
<td>Choi 2007</td>
<td>570</td>
<td>0/1.9</td>
<td>58</td>
<td>2.6</td>
</tr>
</tbody>
</table>

Adapted from Lau et al, Ann Surg 2009

### TACE-RFA as Primary Treatment of Unresectable HCC

- 291 pts w/ HCC >3 cm randomized to either TACE-RFA, RFA alone or TACE alone

<table>
<thead>
<tr>
<th></th>
<th>TACE-RFA</th>
<th>RFA Alone</th>
<th>TACE Alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Survival</td>
<td>37</td>
<td>22</td>
<td>24</td>
</tr>
<tr>
<td>(months)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Objective Response</td>
<td>54</td>
<td>36</td>
<td>36</td>
</tr>
<tr>
<td>&gt; 6 months (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Cheng et al, JAMA 2008

### RFA for HCC

**Summary**

- 1st line treatment for small HCC
  - preferably 3 cm or less, 5 cm maximum
  - pts not candidates for transplant or resection
- Comparable short-term outcomes to resection for small tumors (3 cm or less) in resectable pts
- More effective than other local ablative therapies
- Other possible uses requiring more study:
  - Bridging therapy before transplant
  - Treatment of recurrence
Hepatocellular Carcinoma
Chemoembolization (TACE)

- Not considered curative
  - Prolongs survival
- Bridge to resection or transplant
- Primary therapy in pts who are not resection or transplant candidates
- Appropriate for large and hypervascular tumors

TACE as Primary Treatment of Unresectable HCC

<table>
<thead>
<tr>
<th></th>
<th>TACE</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Pts</td>
<td>40</td>
<td>39</td>
</tr>
<tr>
<td>Overall Survival (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-Yr</td>
<td>57</td>
<td>32</td>
</tr>
<tr>
<td>2-Yr</td>
<td>31</td>
<td>11</td>
</tr>
<tr>
<td>3-Yr</td>
<td>26</td>
<td>3</td>
</tr>
</tbody>
</table>

Lo et al, Hepatology 2002

Case 6
60y/o M with hepatitis B, no cirrhosis, preserved liver function, and a large liver mass. AFP = 3000.
The next step in management is:

a) Biopsy and sorafenib
b) Biopsy then resection
c) No biopsy; immediate resection
d) No biopsy; TACE then resection if good response
e) No biopsy; TACE then RFA

Case 6 Follow-Up

- Underwent serial TACE
- AFP down to 110
- Extended rt hepatectomy w caudate resection
  - Path: 13.5 cm HCC, 90% necrosis, no LVI
- 2+ years NED

HCC
Results By Treatment Modality

- 1366 patients w HCC and chronic hepatitis, 1991-2004, Univ Hong Kong

From Chan et al, Ann Surg 2008
Peripheral Intrahepatic Cholangiocarcinoma

- Primary therapy is liver resection
- Survival s/p resection:
  - median 8-50 months
  - 5-yr 13-44%
- Prognostic factors:
  - LVI
  - Regional nodal mets
  - R1/R2 resection
  - Tumor size

Extra-hepatic Cholangiocarcinoma

Primary Treatment

- Dependent on location of tumor in extra-hepatic bile duct
- Lower 1/3: Pancreaticoduodenectomy
- Middle 1/3: Extra-hepatic bile duct resection with regional node dissection
- Upper 1/3 (Hilar): En bloc hepatectomy with extra-hepatic bile duct resection and regional LND

Extra-hepatic Cholangiocarcinoma

Critical Determinants of Resectability

- Presence of distant metastases
  - Lung, liver, peritoneum
- Vascular involvement
  - Hepatic artery, portal vein
- Extent of tumor within biliary system
- Hepatic lobar atrophy
Hilar Cholangiocarcinoma
Local Criteria for Unresectability

- Main portal vein involvement
- Bilateral duct involvement up to secondary biliary radicals

Hilar Cholangiocarcinoma
Local Criteria for Unresectability II

- Unilateral lobar atrophy with contralateral portal vein involvement
- Unilateral lobar atrophy with contralateral involvement of secondary biliary radicals

Primary Resection for Bile Duct Cancer
Selected Series

<table>
<thead>
<tr>
<th>Series</th>
<th>Number of Patients</th>
<th>5-Yr Survival (%)</th>
<th>Median Survival, mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jarnagin 2001</td>
<td>80</td>
<td>27</td>
<td>35</td>
</tr>
<tr>
<td>Rea 2004</td>
<td>46</td>
<td>26</td>
<td>28</td>
</tr>
<tr>
<td>Zervos 2004</td>
<td>31</td>
<td>26</td>
<td>--</td>
</tr>
<tr>
<td>Jang 2005</td>
<td>151</td>
<td>32</td>
<td>27</td>
</tr>
<tr>
<td>Hemming 2005</td>
<td>53</td>
<td>35</td>
<td>40</td>
</tr>
<tr>
<td>Nagino 2006</td>
<td>132</td>
<td>27</td>
<td>--</td>
</tr>
<tr>
<td>Murakami 2007</td>
<td>43</td>
<td>44</td>
<td>26</td>
</tr>
<tr>
<td>Baton 2007</td>
<td>59</td>
<td>20</td>
<td>--</td>
</tr>
</tbody>
</table>
Liver Directed Therapy

Summary

• Hepatic resection clearly of value in metastatic colorectal cancer
  – Few absolute contra-indications
• Evidence favors resection for metastatic NET
• Consider resection for other metastatic tumors with evidence of favorable tumor biology
• Multiple approaches for HCC