A Multidisciplinary Approach to Liver Tumors

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Disclosures

• None
Learning objectives

• Describe how the successful management of liver tumors involves care from multiple disciplines working in close coordination.

• Discuss some of the treatment strategies for liver tumors and how a customized treatment plan is developed.
• A broad differential of benign and malignant conditions manifest as liver tumors

• Depending on the radiographic and pathologic characterization, these tumors may need nothing more than reassurance….
  • Or surveillance…
  • Or biopsy…
  • Or surgery…
  • Or chemo-embolization….
  • Or radio-embolization…
  • Or ablation…
  • Or chemotherapy…
  • Or transplant…
  • Or palliation
Liver Tumors

- Which means a variety of disciplines have unique expertise to bring to such cases.

  - Or surveillance...
  - Or biopsy...
  - Or surgery...
  - Or chemo-embolization…
  - Or radio-embolization…
  - Or ablation…
  - Or chemotherapy…
  - Or transplant…

  - Radiology/Hepatology
  - IR/surgery
  - Hepatobiliary Surgery
  - IR
  - Radiation Oncology
  - IR/surgery
  - Medical Oncology
  - Transplant Surgery/Hepatology
Multidisciplinary Approach

• Capitalizes on the expertise of multiple disciplines
  • “It is like having 10 doctors see you at once”
  • Multidisciplinary tumor board
  • Multidisciplinary clinic
Workflow

• Starts with referral to a specialist
  • Hepatology/GI
  • Surgical Oncology
  • Transplant Surgery
  • Medical Oncology
Referral and clinical evaluation by specialists

High quality diagnostic imaging (MRI vs. Liver Protocol CT)

- Review with dedicated liver radiologists
- Presentation at multidisciplinary tumor board

Imaging is diagnostic

- Benign
  - Asymptomatic: Observation
  - Symptomatic

Imaging is non-diagnostic

- Malignant
  - Treatment
  - Serial Imaging
  - Biopsy
Workflow

• Appropriate imaging
  • Liver protocol CT
  • Contrast enhanced MRI
    • MRCP
    • Eovist
Workflow

- Discussion in multidisciplinary tumor board
  - Hepatology
  - Transplant Surgery
  - Radiology
  - Surgical Oncology
  - Medical Oncology
  - Radiation Oncology
  - Interventional Radiology
Tumor board in the real world
Diagnostic/Therapeutic Plan

- Benign finding/asymptomatic
  - Reassurance

- Possible malignancy
  - Repeat or alternative imaging
  - Percutaneous or surgical biopsy

- Benign symptomatic mass or high concern for malignancy
  - Resection
  - Ablation
  - Transarterial chemo-embolization
  - Radioembolization
  - External Beam Radiation
  - Chemotherapy
  - Sorafenib
  - Transplant
Benign lesions

- Adenomas
- Fibronodular hyperplasia (FNH)
- Hemangioma
- Cysts
Adenomas

• May be associated with hormone therapy (steroids, OCPs, hormone replacement)
• Low metastatic potential
• Bleeding risk when large
• Can be differentiated from FNH with Eovist MRI
• Stop all OCPs or hormone replacement therapy
• May benefit from therapy when large or symptomatic
  • Resection
  • Bland embolization
FNH

- Low malignant potential
- Can look similar to adenomas
  - Sometimes have a central scar
  - Retains eovist on delayed imaging
- Rarely requires intervention
  - Surveillance warranted if size is increasing.
Hemangioma

- Benign vascular tumor
- Low malignant potential
- Can cause symptoms related to pressure on adjacent organs or proximity to liver capsule
- Intervention rarely indicated unless symptomatic
Hepatocellular Carcinoma

• Most common primary hepatic malignancy
• Common in cirrhosis, particularly HCV
• Has characteristic findings on contrast enhanced CT or MRI
  • Can be associated with elevated AFP
  • Biopsy can be usually be avoided with high quality liver protocol cross-sectional imaging
Hepatocellular Carcinoma (HCC)

Approximately 20,000 new cases and deaths
5th leading cause of cancer-related death in US

Figure 2. Age-Adjusted Incidence and 5-Year Survival Rates for Patients with Hepatocellular Carcinoma in the United States, 1973–2007.

El-Serag HB. NEJM 2011.
HCC diagnosis

- Liver protocol imaging highly sensitive/specific for HCC
  - Arterial enhancement
  - Venous phase washout
  - Pseudocapsule
  - Interval growth in a suspicious mass
- Still a role for biopsy in select cases of indeterminant radiographic findings.
- AFP can be elevated
CT/MRI LI-RADS® v2017 CORE

Untreated observation without pathologic proof in patient at high risk for HCC

If cannot be categorized due to image degradation or omission → LR-NC
If definite tumor in vein (TIV) → LR-TIV
If definitely benign → LR-1
If probably benign → LR-2
If probably or definitely malignant but not HCC specific (e.g., if tergetoid) → LR-M

Otherwise, use CT/MRI diagnostic table below

If intermediate probability of malignancy → LR-3
If probably HCC → LR-4
If definitely HCC → LR-5

CT/MRI Diagnostic Table

<table>
<thead>
<tr>
<th>Arterial phase hyperenhancement (APHE)</th>
<th>No APHE</th>
<th>APHE (not rim)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observation size (mm)</td>
<td>&lt; 20</td>
<td>≥ 20</td>
</tr>
<tr>
<td>Count major features</td>
<td>None</td>
<td>LR-3</td>
</tr>
<tr>
<td>• “Washout” (not peripheral)</td>
<td>One</td>
<td>LR-3</td>
</tr>
<tr>
<td>• Enhancing capsule</td>
<td>≥ Two</td>
<td>LR-4</td>
</tr>
</tbody>
</table>

Observations in this cell are categorized LR-4, except:
- LR-5g, if ≥ 50% diameter increase in ≤ 6 months (equivalent to OPTN 5A-g)
- LR-5us, if “washout” and visibility at screening ultrasound (per AASLD HCC criteria)

If unsure about the presence of any major feature: characterize that feature as absent
HCC treatment

• Resection is treatment of choice but....
  • Limited by underlying cirrhosis
  • Disease is often multifocal/bilobar
  • Pros
    • Can be curative if disease if unifocal
    • Can be tolerated if low volumes are removed in Childs A cirrhotics
  • Cons
    • Dangerous in decompensated cirrhosis
    • Does not treat underlying cirrhosis
Transplantation is the preferred modality for patients with limited disease but who would not tolerate resection because of anatomy or cirrhosis.

Milan Criteria

- 4 year survival of 75%
  - Single mass ≤ 5cm in diameter
  - ≤ 3 masses ≤ 3cm in diameter
  - No vascular invasion
  - No nodal or distant metastasis

Mazzaferro, et al. NEJM 1996
Exception points

• Patients with malignancy have risk of mortality not captured by MELD

• HCC patients qualify for exception points:
  • Unresectable HCC by radiographic criteria
  • Stage II or lower
  • Satisfy Milan Criteria

• Automatically assigned MELD of 22 with increase of 2 points every 3 months

• After 6 month wait with demonstrated stable disease within Milan criteria, qualify for 28 points with additional points applied every 3 months.

Smith et al, AJT 2012
HCC treatment options

• Resection
• Transplantation
  • Pros
    • Can be an option for single tumors < 5cm or 3 or fewer tumors each less than 3 cm
    • Treats underlying cirrhosis as well as cancer
    • Can get “exception points” that give priority on the waitlist
  • Cons
    • Major operation with substantial morbidity
    • Need for lifetime immunosuppression
    • Need to demonstrate compliance/abstinence of alcohol, drugs and tobacco, as well as social support
    • Often need to wait at least 6 months to get exception points
## State of the Waitlist for Malignancy

<table>
<thead>
<tr>
<th>Primary cause of disease</th>
<th>Level</th>
<th>2001</th>
<th>2011</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute hepatocellular nec.</td>
<td>2001: 815</td>
<td>4.9%</td>
<td>2011: 394</td>
</tr>
<tr>
<td>HBV</td>
<td>2001: 626</td>
<td>3.8%</td>
<td>2011: 430</td>
</tr>
<tr>
<td>HCV</td>
<td>2001: 5,020</td>
<td>30.3%</td>
<td>2011: 4,615</td>
</tr>
<tr>
<td>Alcoholic liver dis.</td>
<td>2001: 3,836</td>
<td>23.2%</td>
<td>2011: 3,563</td>
</tr>
<tr>
<td>Cholestatic disease</td>
<td>2001: 1,877</td>
<td>11.3%</td>
<td>2011: 1,381</td>
</tr>
<tr>
<td>Malignancy</td>
<td>2001: 354</td>
<td>2.1%</td>
<td>2011: 915</td>
</tr>
<tr>
<td>Other/unk.</td>
<td>2001: 4,017</td>
<td>24.3%</td>
<td>2011: 4,049</td>
</tr>
</tbody>
</table>

OPTN/SRTR Annual Report 2011
HCC treatment options

• Ablation
  • Either interventional radiology or surgical approach
  • Either microwave or radiofrequency
  • Pros
    • Outcomes similar to surgery for smaller tumors (up to 3 cm)
    • Well tolerated, even in cirrhotics
  • Cons
    • Sometimes incompletely treats tumors
    • No pathology/margins
    • More risky in tumors located near the liver capsule (rupture or spread)
    • RFA can be less effective for tumors near major venous structures
HCC treatment options

• Trans-arterial chemo-embolization (TACE)
  • Catheter-directed approach that isolates the vessels supplying the tumor and embolize with doxorubicin or cisplatin containing beads
  • Pros
    • Well tolerated, even in decompensated cirrhosis
    • Can be done multiple times or in conjunction with MWA
    • Can treat multiple tumors
    • Can be used as a bridge to transplant
  • Cons
    • Residual disease is common
    • Multiple treatments often required
    • Results inferior to surgery or ablation
HCC treatments

• Radioembolization
  • Transarterial Ytrrium (Y-90) embolization
  • Pros
    • Can treat larger tumors (radio-hepatectomy)
    • Well tolerated
  • Can take several months to work
  • Results inferior to surgery or ablation
HCC treatment options

• Sorafenib (Nexivar)
  • Tyrosine kinase inhibitor
  • Indicated for unresectable HCC
  • Pros
    • Well tolerated oral agent with minimal side effects
    • Has been shown to extend survival ~ 3months
  • Cons
    • Not curative
... in the real world...

- Often a combination
  - TACE combined with ablation
  - Liver directed therapy combined with transplant evaluation
  - Ablation combined with Y-90
  - Sorafenib if not a candidate for other therapies
Other Liver tumors

• Primary malignancies
  • Cholangiocarcinoma
    • Intrahepatic
    • Hilar
    • Extrahepatic

• Metastatic disease
  • Colorectal cancer metastasis
  • Neuroendocrine cancer metastasis
Cholangiocarcinoma

- Primary tumor of the bile duct epithelium
- Often difficult to diagnose via radiology or biopsy
  - High index of suspicion required
  - Associated with cholestatic disease of the liver
    - PSC/PBC
  - Can be associated with elevated CA 19.9 levels
Cholangiocarcinoma

- Difficult to obtain tissue diagnosis
  - High index of suspicion required
  - ERCP/brushings or clamshell biopsies often indeterminate
- Biopsy?
  - Concern for seeding of the tract, but a skilled interventionalist can minimize risk
- Consider resection for suspicious mass
Cholangiocarcinoma treatment

• Surgical resection is the only curative therapy for cholangiocarcinoma
• Often unresectable at time of diagnosis
• Transplant has been used in select cases of unresectable hilar cholangiocarcinoma
• Adjuvant chemotherapy depending on node status/Stage.
Liver Transplantation for Cholangiocarcinoma

• Dismal outcomes with conventional therapy

• CCA is in some ways similar to HCC
  • Primary hepatic malignancy
  • Often occurs in a background of chronic liver disease (PSC/PBC)

• Liver transplantation has been attempted in selected patient
  • Perihilar ECC and select ICC
  • Unresectable
  • Node negative
  • PSC
Protocol

71
- Cholangiocarcinoma
  - External Beam Radiation
  - Intrabiliary Brachytherapy

64
- Oral Capecitabine (Xeloda)

38
- Operative Staging
- Liver Transplantation

5 deaths
1 awaited staging
14 excluded from Tx
9 awaited Tx

Rea et al, Ann Surg 2005
Experience

Among all 71 patients who started protocol 1, 3, and 5 year survival was 79%, 61%, and 58%.

Of those who underwent transplantation, 1, 3, and 5 year survival was 92%, 82%, and 82%.

FIGURE 1. Patient survival from start of neoadjuvant therapy (all 71 patients in transplant protocol) or resection.
Metastatic Colorectal Cancer

- Patients with stage 4 colorectal cancer with liver metastases (CRLM) derive a survival benefit to aggressive treatment
  - ~50% 5-year survival with resection.
- Surgical resection can be non-anatomic resections or formal hepatectomies
- Percutaneous or surgical ablation is also very useful, with outcomes similar to surgery
Guidelines

• All patients with CRLM should be discussed in a multidisciplinary committee
• Goal for resection is to remove all macroscopic disease with negative margins and leave sufficient functioning liver
• Patients should not be considered for hepatectomy unless primary tumor is resectable
• Ablation or stereotactic external beam radiation may be an alternative for unresectable disease or unfavorable resection candidates
• Borderline or unresectable cases should be reevaluated at 2 month intervals during adjuvant chemotherapy to assess response and potentially convert to resectable disease.
Considerations

- Role of neoadjuvant and adjuvant chemoradiation
  - Chemotherapy induced hepatotoxicity is a major consideration when evaluating how much healthy liver remains after resection

- Portal vein embolization
  - Can encourage hypertrophy of the functional liver remnant (FLR)

- 2-stage hepatectomy
  - Also gives time for liver to hypertrophy

- Combination resection and ablation
  - Can be performed simultaneously in the OR

- Consider simultaneous resection of primary tumor and oligometastatic disease
  - May have higher infectious complication rate
Metastatic Neuroendocrine

- Often indolent course
- Can benefit from resection, ablation or embolization
- Select cases can benefit from transplantation.
Liver-Directed Treatment for NELM

- Neuroendocrine tumors (NET) are rare but metastasize to the liver in up to 44% of patients

- Indolent natural history, even in the setting of metastatic disease
  - Possible morbid hormonal symptoms

- Hepatic resection remains the only therapy with potential for cure for patients with NELM
  - 15-50% of patients eligible for hepatectomy or thermal ablation

- Liver failure is rare despite tremendous disease bulk

Chamberlin RS et al. JACS 2000.
Summary of Liver-directed Therapies for NELM

- Indolent disease with high long-term survival balanced with a near universal recurrence after hepatic resection

- As compared to CCA, more promising targeted therapeutic options that continue to mature in ongoing clinical trials

- Balance of repeat operations and interventions with disease burden, patient symptoms and quality of life

- Thoughts to consider before OLT for NELM:
  - It’s a metastatic disease, the majority of which is confined to the liver
  - A 50% 10-year survival, even with near universal recurrence is difficult to beat
  - Multiple interventions/operations before they are deemed unresectable
The Long-Term Benefit of Liver Transplantation for Hepatic Metastases From Neuroendocrine Tumors

Screened liver mets from NETs referred for liver transplant (n=280)

Patients suitable for curative surgery (n=75)
Curative resection of both primary tumor and liver metastases

1st round exclusion
Patients unsuitable for curative surgery (n=65)
- Pts not eligible to surgery for primary tumor, extensive extrahepatic spread, metastases on multiple sites, high peri-operative (ASA) risk: n=56
- Pts eligible to T or M resection but presenting with peritoneal diffusion (carcinoma): n=9

Liver mets from NETs suitable for liver transplant (n=140)

2nd round exclusion
Patients exceeding transplant criteria (n=52)
- Age > 60 (n=24)
- Co-morbidity incompatible with transplantation (n=13)
- Progression while screened (n=12)
- Other causes (n=3)

Liver mets from NETs eligible to liver transplant (n=88)

Waiting list decision (Multidisciplinary Board)
based on list dynamics, patient compliance and age considerations

GROUP 1
Transplant (n=42)
- No Transplant (n=46)
  - non compliance, refusals (n=22)
  - transplant list unavailability (n=24)

GROUP 2

Mazzaferro1,*, C. Sposito1, J. Coppa1, Miceli2, S. Bhoo1, M. Bongini1, T. Camerini2, Milione3, E. Regalia1, C. Sprefico4, Gangeri5, R. Buzzoni6, F. G. de Braud6, De Feo7 and L. Mariani2
The Long-Term Benefit of Liver Transplantation for Hepatic Metastases From Neuroendocrine Tumors

• Patients
  • Subgroup of patients ineligable for resection
  • Young (age<60)
  • Few comorbidities
  • Primary tumor resected

• Results
  • Large overall and disease free survival benefit to transplantation
  • Largest effect was in younger candidates.
• Resection/Liver directed therapy
  • Indolent disease with high long-term survival balanced with a near universal recurrence after hepatic resection
  • As compared to CCA, more promising targeted therapeutic options that continue to mature in ongoing clinical trials
  • Balance of repeat operations and interventions with disease burden, patient symptoms and quality of life
• Transplant
  • Curative intent
  • Can be considered for patients with low-grade gastrointestinal primary tumors
  • In selected candidates has excellent survival
  • Is not automatically granted exception points under current UNOS/OPTN policy (but you can still request them)
Conclusions

• Most liver tumors can benefit from the expertise of a multidisciplinary approach
• Optimal treatment often involves a staged diagnostic and therapeutic approach that balances curative intent with therapeutic morbidity
• Close coordination and ongoing discussion of cases to determine response to therapy and future options and eligibility for clinical trials is essential.
QUESTIONS?