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Hepatocellular Carcinoma and Cholangiocarcinoma

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Objectives

- Review epidemiology of cholangiocarcinoma (CCA) and standard of treatment options
- Review epidemiology of primary hepatocellular carcinoma (HCC)
- Describe ABCs of treatment and outcomes of HCC
- Discuss surveillance and diagnostic approaches for HCC
- Compare surgical resection, liver transplant, and ablative techniques in HCC
Cholangiocarcinoma (CCA)

- Tumor of the bile duct epithelium
- Incidence in US 1.2:100,000
- Classified according to location
  - Intrahepatic (iCCA) ~ 5-10%
    - Survival dependent on extent of disease at presentation
  - Extrahepatic (pCCA), ~ 90%, mainly perihilar
  - Mixed HCC and CCA
- Associated with poor prognosis

Treatment Options for CCA

- Current standard treatment is resection
- Advances in operative techniques have improved outcomes
- Resection for pCCA associated with 5 year survival of 25-40%
- Survival of iCCA depends on extent of disease at presentation
- No benefit of resection with metastatic disease
- Liver transplant (LT) may be option if unresectable but confined to the liver

LT for CCA

• pCCA
  – LT initially contraindicated
  – Early stage, unresectable disease after neoadjuvant chemoradiotherapy followed by LT demonstrated 5 year disease free survival ~ 65%
  – Diagnostic selection criteria required for centers with specific protocols

• iCCA
  – Treatment of choice is resection
  – Early stage (single tumor ≤ 2 cm) in cirrhotics may benefit from LT
  – Advanced stage in unresectable non-cirrhotics may benefit from LT if stable after neoadjuvant therapy
  – LT reserved for unresectable cases under strict protocols or trials
Mixed HCC-CC

- Hepatic progenitor cells can give rise to hepatocytes and cholangiocytes
- Diagnosis can be difficult
- Imaging of HCC-CC is challenging
  - No pathognomonic pattern
- Tend to behave more aggressively than HCC alone
- Atypical HCC cases may warrant biopsy
- Limited experience and no consensus for LT

Primary Hepatocellular Carcinoma (HCC)

- 5th most common cancer worldwide
- Incidence rising in the US
  - Males higher prevalence (2:1 - 4:1)
  - Age of diagnosis is higher in females
  - Highest incidence: Hispanics > Black > Caucasian
- Arises from pre-existing cirrhosis in >80%
- Tumor characteristics permit highly accurate imaging diagnosis without biopsy

The ABCs

• Treatment and outcome of hepatocellular carcinoma depend on the ABC’s: Anatomic stage, Biological aggressiveness and Cirrhosis severity

• Early stage lesions with good biology in patients with good liver function can be cured by thermal ablation, resection, or liver transplantation

• Choice of approach improved by multidisciplinary consensus, including transplant center
Survival of HCC

- Determined by the ABC’s:
  - Anatomy (stage)
    - Size and number of intrahepatic lesions
    - Presence of nodal or hepatic metastases
  - Biology (grade)
    - Histological features of poor differentiation
    - Vascular invasion
    - Rapid growth and high metabolic rate
  - Cirrhosis severity and performance status
    - May define prognosis
    - Limits treatment options
BCLC Staging and Treatment

Very early stage (0)
- Single <2 cm
- Preserved liver function
- PS 0

Early stage (A)
- Solitary or 2-3 nodules <3 cm
- Preserved liver function
- PS 0

Intermediate stage (B)
- Multinodular, unresectable
- Preserved liver function
- PS 0

Advanced stage (C)
- Portal invasion/extrahepatic spread
- Preserved liver function
- PS 1-2

Terminal stage (D)
- Not transferable HCC
- End-stage liver function
- PS 3-4

Prognostic stage

Treatment
- Ablation
- Resection
- Transplant
- Ablation

Survival
- >5 years
- >2.5 years
- ≥10 months
- 3 months

PS = performance status; BSC = best supportive care.
EASL, 2018.
Summary: Management of HCC

- Liver transplantation
- Resection
- Imaging guided interventions
  - Percutaneous ethanol injection (PEI)
  - Radiofrequency thermal ablation (RFA)
  - Chemoembolization (TACE)
  - Radioembolization (TARE)
  - Yttrium
  - External beam radiation
- Systemic chemotherapy
Surgical Option: Resection

- BCLC Stage 0, preserved liver function
- In early stage HCC, ability to tolerate curative resection is determined by normal liver function (bilirubin) and absence of portal hypertension
- 5 year survival was 74% after resection in patients with neither portal HTN nor jaundice
- While HCCs are increasing rapidly, liver transplantation rates are not

Reducing death from HCC will require greater use of non-transplant curative therapies

Surgical Option: Liver Transplant

- BCLC Stage 0-A and otherwise candidates for transplant
- 60-70% five year survival
- Prior to Milan Criteria
  - 5YS 44%; half of deaths related to tumor recurrence
  - Risk factors for recurrence/death
    - Tumor > 5 cm
    - Vascular invasion
    - Histological grade
    - Positive nodes

Liver Transplant Outcomes
- Only 4/48 recurred (8%)
- 4 YS 75%

By explant path, 13 (27%) had been under-staged
- These patients had poorer 4YS (50%) than patients whose path remained within Milan criteria (4YS 85%)

Led to renewed enthusiasm for transplantation for HCC

Anatomical HCC staging: TNM

Stage I  Single lesion < 2 cm

Stage II  Single lesion 2 – 5 cm OR
          up to 3 lesions, largest < 3 cm

Stage III Up to 3 lesions, beyond stage II

Stage IV  4 or more lesions, any size
Tumor venous invasion
Nodal or distant metastasis

The Milan Criteria
Downstaging and Liver Transplant

- Liver transplantation for HCC with MELD exception requires tumors within Milan criteria
- Subsequent studies find that some HCC beyond Milan criteria can be transplanted successfully
- Approach is termed “downstaging” and involves:
  - Ablation of stage III primary tumors
  - Follow-up imaging showing locoregional control with absence of progression
  - Reclassify as stage II → list for LT w MELD exception
- Key concept: “ablate and wait” approach allows distinction of indolent from aggressive HCC and selects patients with best prognosis for LT
- TACE and Y-90 are widely used to shrink tumors (downstage) and prevent progression prior to LT
Ablative Techniques

- Thermal types:
  - Radiofrequency
  - Microwave
  - Cryoablation

- BCLC Stage 0-A and tumors not amenable for surgery

- 40-70% five-year survival
Thermal Ablation: RFA

- Electric Current
- Applies a high frequency alternating current (in the range of 350–500 kHz)
- Advantages over earlier electrical ablation methods
- Best when tumors are:
  - Small (< 2-3 cm)
  - Single
  - Slow growing

RFA: Surgical vs. Percutaneous

- Open or laparoscopic
- Approach maybe better if:
  - Lesions adjacent to diaphragm, gallbladder
  - Hard to reach sites (dome)
- Intraoperative US used to identify and target lesions
- Adds surgical risk
  - Post-op ascites
  - Incisional hernias

- Technical limitations
  - Tumor anatomy
    - Size > 3 cm (possible up to 5 cm)
    - Hard to reach location
    - Hard to visualize by CT or US
    - Critical adjacent structures risk thermal injury
    - Proximity to large vessels (heat sink)
    - Liver surface lesions

- Complications
  - Pain
  - Tissue necrosis → SIRS
  - Infection/abscess
  - Needle track seeding
Thermal Ablation: MCW

- Kills tumor by heating tissue with microwaves (electromagnetic)
- Approach, application similar to RFA
- Advantages
  - Easier targeting, more predictable
  - Homogenous treatment effect
  - Slightly larger tumors
  - Less “heat sink” effect of adjacent vessels
  - Less painful

Thermal Ablation: Cryoablation

- Uses hollow needles with tip cooled by circulating liquid nitrogen or argon
- “Ice ball” forms around tip, enveloping surrounding tumor
- Individual ice ball may be up to 6 cm; multiple probes can be used for larger tumors
- Advantages:
  - Preserves architecture
  - Ice ball is highly visible so precise margins of necrosis can be identified on CT or US
  - Allows treatment of peripheral or capsular lesions with minimal pain

G Rong et al. 2015.
Outcomes After Cryoablation for HCC

- **Survival**
  - 5 yr survival was 60%
    - 64% of deaths were due to HCC, 36% due to cirrhosis

- **Overall recurrence 60%**
  - Most recurrences were at new intrahepatic sites distant from the original tumor
  - Predictors of local recurrence
    - Multiple tumors
    - Tumor > 3 cm
    - Multiple treatment sessions to achieve local ablation

G Rong et al. 2015.
Ablation for HCC: Pros and Cons

• Potentially curative for BCLC Stage 0-A
• Best results with solitary small tumors
• Some lesions may be untreatable due to:
  – Location and size of tumors
  – Proximity to vital structures
  – Severity of liver disease
• Significant procedural morbidity
• Does not cure cirrhosis
• Does not eliminate risk of new HCCs
Summary of Curative Options

- Resection
  - BCLC Stage 0, preserved liver function
  - 70% five-year survival

- Transplant
  - BCLC Stage 0-A and otherwise candidates for transplant
  - 60-70% five-year survival

- Ablation
  - BCLC Stage 0-A and tumors not amenable for surgery
  - 40-70% five-year survival
Conclusions

• Survival of CCA depends on location and extent of disease at presentation
• Liver transplant may be an option in unresectable CCA confined to the liver
• Some HCC can be cured by liver transplantation (stage 0-A), resection (stage 0) or RFA (stage 0-A)
• Likelihood of success depends on the ABC’s:
  – Anatomic stage: early
  – Biology: indolent (low grade)
  – Cirrhosis: well compensated
• As transplant availability shrinks, saving more lives requires that we make better use of non-transplant curative alternatives for HCC & CCA
Discussion and Questions