



# GHAPP

Gastroenterology & Hepatology  
Advanced Practice Providers

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**GHAPP**

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# Hepatocellular Carcinoma and Cholangiocarcinoma

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# Disclosures

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No financial relationships to disclose.

# Objectives

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- 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  $\leq 2$  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)

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- 5<sup>th</sup> 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

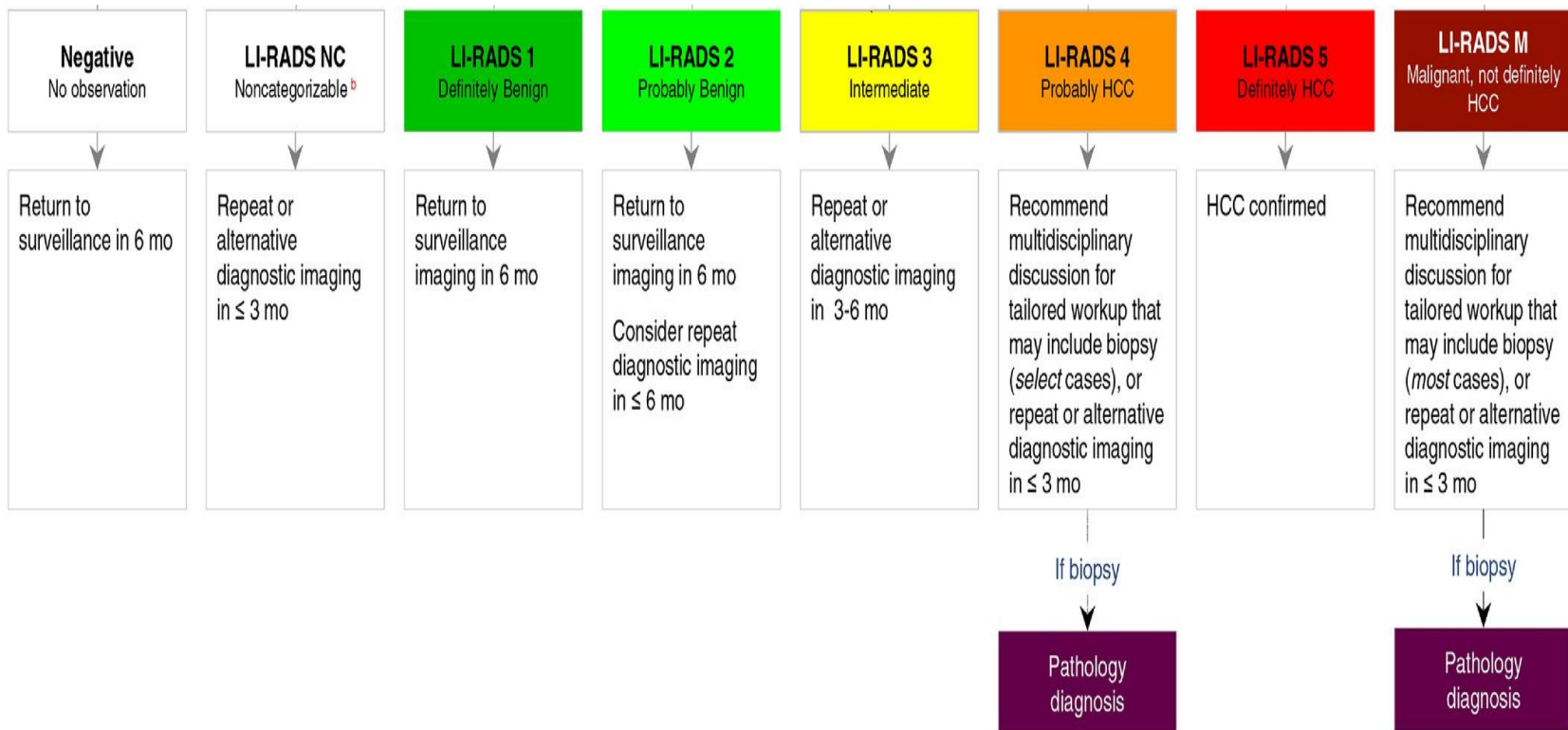
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- Treatment and outcome of hepatocellular carcinoma depend on the ABC's: Anatomic stage, Biological aggressiveness and Cirrhosis severity
- Early stage lesions with good biology in patients with good liver function can be cured by thermal ablation, resection, or liver transplantation
- Choice of approach improved by multidisciplinary consensus, including transplant center

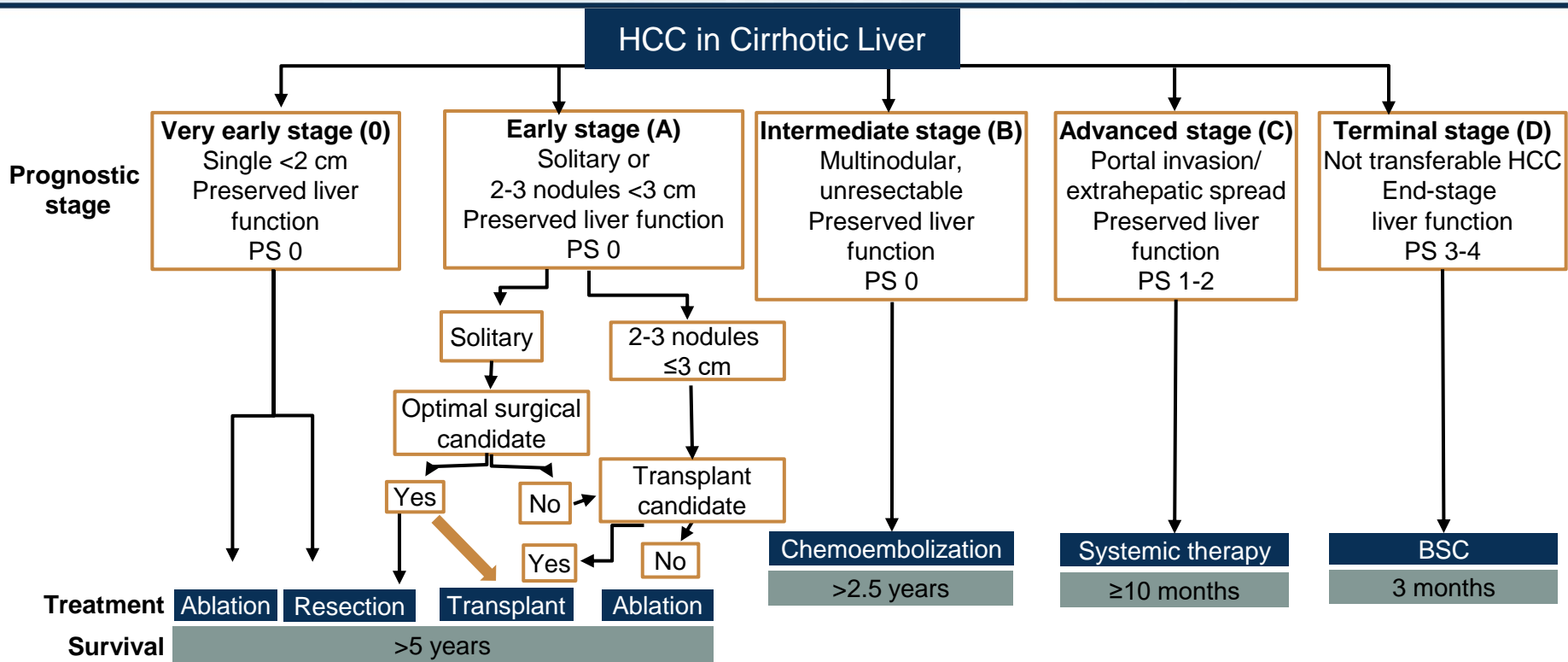
# Survival of HCC

- 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

# AASLD Surveillance and Diagnostic Algorithm



# BCLC Staging and Treatment



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

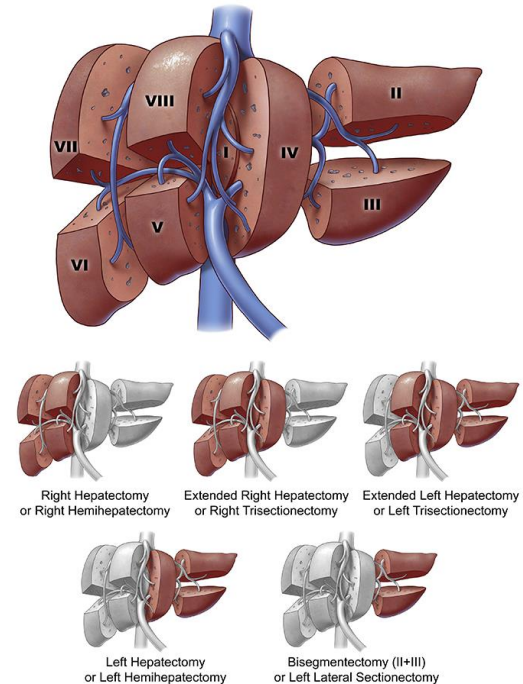


**Potentially  
curative**

# 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

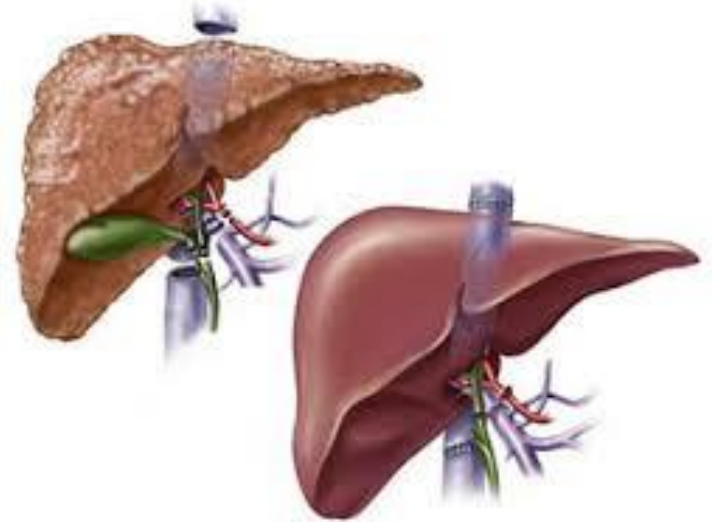
*Reducing death from HCC will require greater use of non-transplant curative therapies*





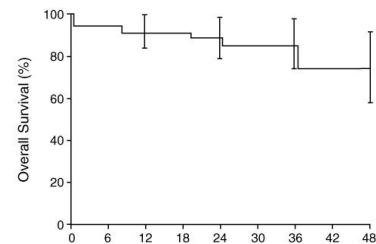
# Surgical Option: Liver Transplant

- 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



# The Milan Paper

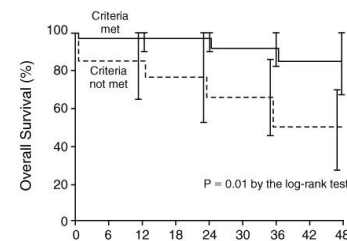
- Liver Transplant Outcomes
  - Only 4/48 recurred (8%)
  - 4 YS 75%
- By explant path, 13 (27%) had been under-staged
  - These patients had poorer 4YS (50%) than patients whose path remained within Milan criteria (4YS 85%)
- Led to renewed enthusiasm for transplantation for HCC



A

PATIENTS AT RISK

Months after Transplantation	0	6	12	18	24	30	36	42	48
PATIENTS AT RISK	48	45	40	32	27	21	17	9	5



A

PATIENTS AT RISK

Months after Transplantation	0	6	12	18	24	30	36	42	48
Criteria met	35	34	31	24	21	16	13	6	3
Criteria not met	13	13	11	8	6	6	4	4	3

# 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

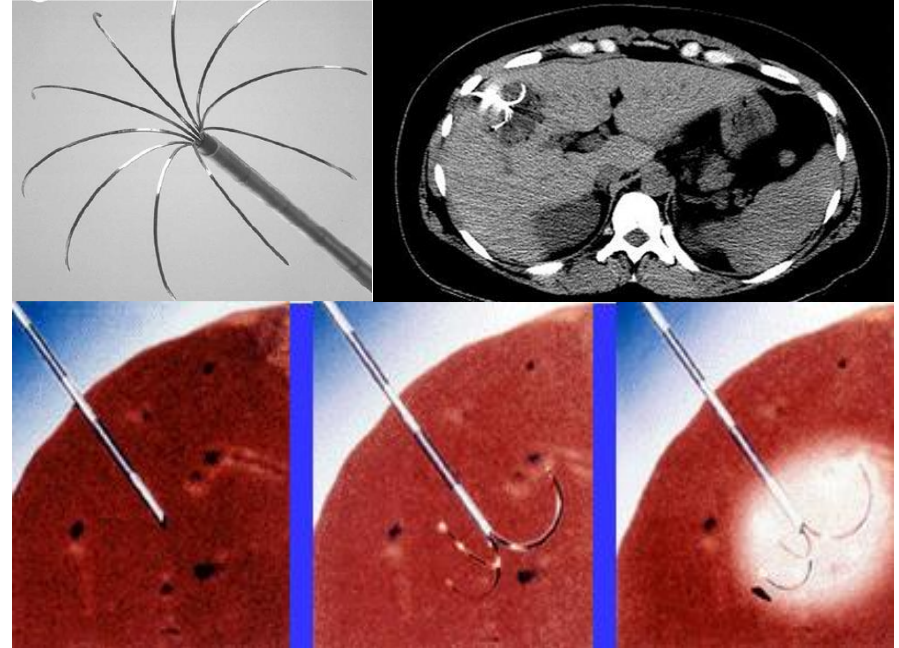
- Liver transplantation for HCC with MELD exception requires tumors within Milan criteria
- Subsequent studies find that some HCC beyond Milan criteria can be transplanted successfully
- Approach is termed “downstaging” and involves:
  - Ablation of stage III primary tumors
  - Follow-up imaging showing 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

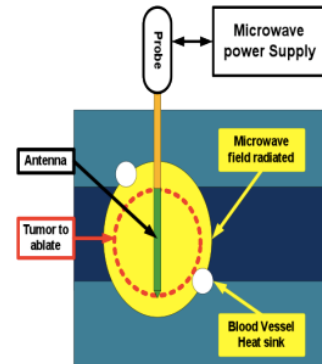


# RFA: Surgical vs. Percutaneous

- 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





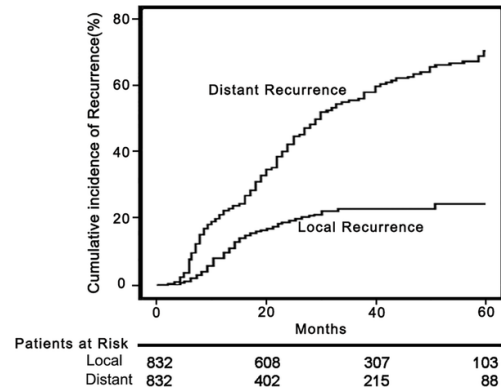
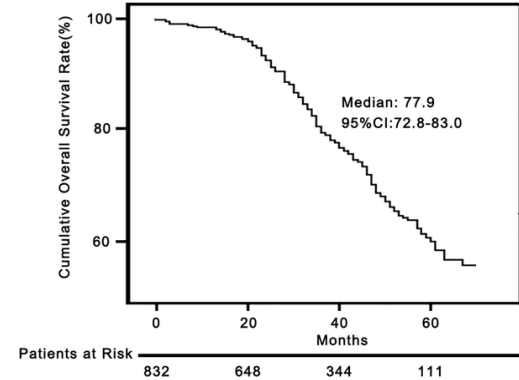
# Thermal Ablation: Cryoablation

- 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



# 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



# Ablation for HCC: Pros and Cons

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- 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

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- 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

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- 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

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