THE BEFORE AND AFTER
HEPATOCELLULAR CARCINOMA MANAGEMENT

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HISTORICAL PERSPECTIVE

- 1980s: Dismal outcome after liver transplantation for large HCC
- Incidental HCC (1-2 cm) had no adverse impact on survival after liver transplantation
- 1993: Bismuth reported better survival after liver transplantation than resection for \( \leq 3 \) lesions \( \leq 3 \) cm
- 1996: Milan criteria: 5-yr patient survival 70-80%
- 2002: MELD system of organ allocation
- 2010: Refinement of transplant criteria and defining the role of adjuvant and loco-regional therapy

MULTIDISCIPLINARY LIVER TUMOR BOARD

PARTICIPANTS
- Hepatologists
- Liver surgeons
- Interventional radiologists
- Radiologist - Abdominal imaging
- Oncologists

OBJECTIVES
- Diagnosis and staging
- Develop treatment strategies

HCC – RADIOLOGIC DIAGNOSIS

Arterial Phase Enhancement
Portal Venous phase “washout”
**DIAGNOSTIC CRITERIA FOR HCC (AASLD Guidelines)**

**Tumor > 2 cm** - One imaging (CT/MRI) showing typical HCC characteristics*

**Tumors 1-2 cm** - Two imaging (CT/MRI) showing typical HCC characteristics*

Liver biopsy recommended if imaging criteria not met

* Arterial phase hypervascularity and delayed phase “washout”

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**HCC – IS BIOPSY NECESSARY?**

Biopsy not always necessary to confirm diagnosis of HCC if the lesion meets radiologic criteria in the appropriate clinical setting

*False negative biopsy common in clinical practice and may lead to delay in diagnosis and treatment*

*Tumor seeding along the biopsy tract in 1-5 %

Biopsy in selected cases if atypical radiologic appearance or lack of strong risk factor for HCC

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**LIVER TRANSPLANTATION FOR HCC**

**MILAN CRITERIA**

1 lesion ≤ 5 cm

2 to 3, none > 3 cm

+ Absence of Macroscopic Vascular Invasion

Absence of Extra-hepatic Spread


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**MELD ALLOCATION SYSTEM FOR HCC**

T2 = 1 lesion 2-5 cm, 2-3 lesions ≤ 3 cm

T1 = 1 lesion ≤ 2 cm

Patients eligible for upgrade of MELD score every 3 months on waitlist

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2002 2003 2004 2005

YR

MELD 29

MELD 24

MELD 20

MELD 22

MELD 24

MELD 20
PRE-TRANSPLANT MANAGEMENT OF HCC
INTENTION-TO-TREAT OUTCOME

肝脏移植
死亡
HCC
T2
等待名单
退出（肿瘤）
死亡
生存和HCC复发
MELD

下文是两个图的描述。

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UCSF CRITERIA

肝脏
1个肿瘤 ≤ 6.5 cm
2到3个，没有 > 4.5 cm
总直径 ≤ 8cm

Yao et al. Hepatology 2001;33:1394-1403

下文是两个图的描述。
LOCO-REGIONAL THERAPIES FOR HCC

CHEMOEMBOLIZATION
Conventional versus Drug-eluting beads

ABLATIONS
CHEMICAL
Percutaneous ethanol injection (PEI)

THERMAL
Radiofrequency ablation (RFA)
(Laparoscopic, percutaneous or open)
Microwave/ Cryo- ablation

RADIOEMBOLIZATION (YITTRIUM - 90)

POTENTIAL ROLES OF PRE-TRANSPLANT LOCOREGIONAL THERAPY

• To slow tumor progression and reduce risk of dropout from the waiting list – “bridge” to liver transplantation.
• To reduce risk of post-transplant HCC recurrence and to improve tumor-free survival after liver transplantation
• “Down-staging” of HCC initially exceeding conventional or acceptable criteria.
LOCOREGIONAL THERAPY FOR HCC TUMOR STAGING AFTER TREATMENT

UCSF DOWN-STAGING PROTOCOL INCLUSION CRITERIA

- No vascular invasion on imaging
- 1 lesion >5 cm and ≤ 8 cm
- 2 or 3 lesions, each ≤ 5 cm with total tumor diameter of all lesions ≤ 8 cm
- 4 or 5 lesions, none >3 cm with total tumor diameter of all lesions ≤ 8 cm

UCSF DOWN-STAGING PROTOCOL
CRITERIA FOR SUCCESSFUL DOWN-STAGING

Residual tumor size and number within UNOS T2 criteria (1 lesion 2-5 cm, 2-3 lesions ≤ 3 cm)

Complete tumor necrosis without residual tumor is equivalent to obliteration of tumor *

* In a patient with 4 lesions, successful down-staging requires obliteration of ≥ 1 lesion so that there are no more than 3 lesions with viable HCC, all ≤ 3 cm to meet UNOS T2 criteria.

UCSF DOWN-STAGING PROTOCOL - RESULTS

- Meets down-staging criteria (n=61)
  - Treatment Failure (n=18) (29.5%)
    - 16 dropouts due to tumor progression and 3 deaths without OLT
  - Treatment Response (n=43) (70.5%)
    - DDLT (n=33)
    - Awaiting DDLT (n=6)
    - LDLT (n=2)

  - 2 censored - 1 had resection and 1 was excluded from OLT for psychosocial reasons

  - Median 8.2 months (3-25 months) from down-staging to OLT
  - Median 7.0 months (1.2-14.2 months) from down-staging to treatment failure

  - 33 patients alive without HCC recurrence, 2 died unrelated to HCC after a median post-transplant follow-up of 25 months

PREDICTORS OF TREATMENT FAILURE

<table>
<thead>
<tr>
<th>Predictor Variables</th>
<th>Hazard Ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multi-focal HCC</td>
<td>0.76 (0.31-1.88)</td>
<td>0.56</td>
</tr>
<tr>
<td>Child’s class B or C</td>
<td>0.97 (0.40-2.40)</td>
<td>0.95</td>
</tr>
<tr>
<td>AFP ≥ 1000 ng/mL</td>
<td>7.75 (2.9-20.7)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>≥ 3 treatments</td>
<td>0.51 (0.18-1.41)</td>
<td>0.19</td>
</tr>
<tr>
<td>Combination treatment</td>
<td>0.67 (0.27-1.66)</td>
<td>0.39</td>
</tr>
</tbody>
</table>


UCSF DOWN-STAGING PROTOCOL
ADDITIONAL GUIDELINES

- Candidates can undergo deceased-donor liver transplant 3 months after down-staging if imaging is favorable with HCC meeting Milan criteria.
- Those with a donor can undergo live-donor liver transplant 3 months after down-staging if imaging is favorable with HCC meeting UCSF criteria.
- Those with acute hepatic decompensation after down-staging are not eligible for transplant unless they meet criteria for successful down-staging.
DOWN-STAGING OF HCC
(UCSF DATA)

- Meeting Milan T2 criteria or complete tumor necrosis
- 2 HCC recurrence
- 84% 5-yr survival post-transplant
- 61% 5-yr intention-to-treat survival

• Successful down-staging can be achieved in the majority of carefully selected patients with HCC exceeding conventional Milan criteria, and is associated with acceptable post-transplant outcome.
• Down-staging allows selection of a subgroup of tumors with more favorable biology that are more likely to respond to treatment and do well after liver transplantation.

DOWN-STAGING INCLUSION CRITERIA
U.S. NATIONAL CONFERENCE

- No vascular invasion on imaging
- 1 lesion >5 cm and ≤ 8 cm
- 2 or 3 lesions, each ≤ 5 cm with total tumor diameter of all lesions ≤ 8 cm
- 4 or 5 lesions, none >3 cm with total tumor diameter of all lesions ≤ 8 cm
- Decrease in AFP to < 500 ng/mL for patients with initial AFP > 1000 ng/mL

THE “ABLATE AND WAIT” CONCEPT

- HCC (Milan T2) → Down-staging → Expanded Criteria
- Ablate and wait
- Dropout
- Liver Transplant
- Dropout

POST-TRANSPLANT HCC RECURRENCE RISK FACTORS

- Tumor size / number > Milan or UCSF criteria
- Vascular invasion (explant)
- Poorly differentiate tumor grade (explant)
- High pre-operative alpha-fetoprotein (AFP)
  New criteria at UCSF: Decrease in AFP to < 500 ng/mL if initial AFP > 1000 ng/mL
- Poor response to loco-regional therapy?
- Other tumor markers?

POST-TRANSPLANT HCC RECURRENCE

- Poor survival after HCC recurrence
- Key = pre-transplant candidate selection to minimize tumor recurrence
- Surveillance after liver transplant - High risk candidates (> Milan; vascular invasion; high AFP) with CT and AFP every 6 months for at least 2 years
- Sorafenib (Nexavar) after liver transplant for patients at high risk for HCC recurrence?

Locoregional Therapy in the Management of HCC

Robert K. Kerlan Jr., M.D.
University of California, San Francisco

Principle of Treatment

- Until proven otherwise, surgical intervention (resection or transplantation) is the only technique proven to cure malignant tumors of the liver
- 5 year survival
  - Resection (colon mets) 20% to 30%
  - Resection (HCC) 40% to 60%
  - Transplantation 80% to 90%
Hepatocellular Carcinoma: Curative Treatment

Catch 22

- Most patients with cirrhosis are not eligible for surgical resection due to limited hepatic functional reserve

Principle of Treatment

- The goal of other treatment modalities should be one of the following:
  - Facilitate resection
  - Prolong survival
  - Relieve symptoms

Interventions Designed to Ablate or Necrose Malignant Tumors

- Arterial therapies
  - Bland or chemoembolization
  - Radioembolization

- Percutaneous ablation
  - Chemical ablation
  - Thermal ablation
    - Radiofrequency
    - Microwave
    - Laser
    - Focused ultrasound
    - Cryoablation

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**Hepatic Chemoembolization**

**Theory**

- Malignant tumors >1 cm derive are fed almost exclusively by hepatic arteries.
- Normal liver gets 75% of its blood supply from the portal vein.
- Therefore, by embolizing the arteries, tumor is destroyed and hepatic parenchyma survives.

**Hepatic Chemoembolization**

**Theory**

- Chemotherapeutic agent combined with embolic material will have:
  - Higher local dose
  - Longer dwell time
  - Diminished systemic effect
  - Take advantage of chemosensitization effect of hypoxia.

**Hepatic Chemoembolization**

**Downside**

- Hypoxia may stimulate angioneogenesis and cause tumor progression.

**Embolic Materials**

- Gelfoam powder
- Polyvinyl alcohol
- Tris-acryl embospheres
- Doxorubicin laden beads
- Ethiodol
Chemotherapeutic Agents

- Cis-platinum
- Adriamycin
- Mitomycin-C

Hepatic Chemoembolization

**Complications**

- Hepatic failure
- Infection
  - hepatic
  - extra-hepatic (gallbladder/bowel)
- Skin necrosis (if parasitized vessels embolized)

Chemoembolization prolongs survival in selected patients with unresectable HCC who have good performance status, reasonable liver function and limited tumor burden.

- Chemoembolization with cis-platin repeated every 2 to 3 months leads to increased survival in unresectable patients with good hepatic function and performance status (1iA).
  
  Lo CM, Ngan H, Tso WK et al. *Hepatology* 2002;35:1164-1171

- Chemoembolization with doxorubicin repeated every 2 to 6 months leads to increased survival in unresectable patients with good hepatic function and performance status (1iA).
  

- Meta-analysis reveals beneficial survival effect for embolization / chemoembolization in comparison to the control group (1iA).
  
  Llovet JM, Bruix J. *Hepatology* 2003;37:429-442
Drug-Eluting Beads

Drug-eluting beads (doxorubicin) may be as effective as “standard” TACE, but may have diminished AEs and SAEs.

- DEB Doxorubicin $C_{max}$ 79 ng/mL compared to conventional TACE $C_{max}$ 2341 ng/mL $p=0.00002$ n=27
  

- RCT 6-month response conventional TACE 52% vs DC Beads 63%
  $p=0.11$. Doxorubicin related side effects conventional TACE 37% vs DC Beads 13% $p=.0001$ n=201


Local Radiation Therapy

- Yttrium-90 labeled beads (TheraSphere, Ontario, Canada) with average diameter of 25 microns
- Pure beta emitter

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Local Radiation Therapy
Radioembolization

No RCTs available comparing \(^{90}\)Y radioembolization to other therapies for moderate and advanced HCCs. Cohort data suggests \(^{90}\)Y radioembolization is moderately effective with acceptable SAEs.

- Partial response 42\%, stable 35\%, progression 23\% by WHO. Response 70\% by EASL. Mean dose 139.7 Gy (n=108)


- AR 0.89 resin vs 0.78 glass (p=0.02 / n=425 / studies=14). Median survival 7.1 to 21.0 months.


Interventions Designed to Ablate or Necrose Malignant Tumors

- Arterial therapies
  - Chemoembolization
  - Radioembolization
- Percutaneous ablation
  - Chemical ablation
  - Thermal ablation
    - Radiofrequency
    - Microwave
    - Laser
    - Focused ultrasound
    - Cryoablation

Available Ablative Therapies

- Variables
  - Routes (percutaneous, laparoscopic, open surgical)
  - Mechanism (chemotoxicity, thermal destruction, membrane alteration)
  - Endpoints (imaging, temperature, impedance, time)
  - Thermal devices (radiofrequency, microwave, cryo, laser, HIFU)

- SAEs
  - Pain
  - Bleeding
  - Non-target ablation (bile duct, diaphragm, GI tract, gallbladder)
  - Sepsis
  - Pleural effusion / ascites
Available Ablative Therapies

- **PEI**
  - Most extensively studied, inexpensive, lowest complication rate, but limited by recurrence or progression for HCCs > 2 cm

- **PAI**
  - Speculated to have improved intratumoral dispersion

- **RFA**
  - Most extensively studied and commonly used thermoablative technique

- **MCT**
  - Potentially larger areas of thermal necrosis with diminished heat-sink effects

- Limited information is available regarding LITT, cryoablation, HIFU, and electroporation.

Percutaneous Ethanol Ablation

Pre EtOH Ablation

1 month post EtOH Ablation

1 year post EtOH Ablation
Adjunctive measures

- Precede with chemoembolization?
- Intratumoral saline injection?
- Intratumoral ethanol injection?
- Intentional pneumothorax for transpleural approaches?
- CO₂ insufflation to protect diaphragm?
- Saline infusion to protect surrounding organs?

Local Ablation: Incomplete Ablation and Recurrence Rate Increases with Size of Lesion

Percutaneous ablation achieves immediate (1 month) complete responses in more than 80% of HCCs ≤ 3 cm, but only 50% in HCCs 3-5 cm in size.

- Initial complete response 96% < 2 cm; 78% 2-3 cm; 56% > 3 cm; 46% 2-3 nodules; 30/282 received TAE + PEI / (p=0.015 main tumor size, p=0.001 tumor stage; n=282) (1iiD)


- Tumor size >3cm is an independent risk factor for incomplete ablation (n=298 pts, 393 HCCs; complete <3cm 95%, complete >3cm 87%; p=0.02)(3D)


- Local recurrence following initially complete RFA was observed in 10% of HCCs < 2.5 cm and 17% > 2.5 cm (p=.039; n=272 pts) (3D)

Lam VW, Ng KK, Chok KSH et al. *J Am Coll Surg* 2008;207:20-29
Locoregional Therapy: Conclusions

- Arterial therapies and ablative therapies are effective in causing tumor necrosis
  - For tumors less than 3 cm in size, locoregional therapy MAY be as effective as surgical resection
  - For larger tumors, residual disease is likely

- In patients with hepatocellular carcinoma, these therapies may be used to “downstage” the patient allowing potentially curative transplantation

- Locoregional therapy is also useful to keep patients listed while awaiting transplantation