Forging Partnerships in the Management of Hepatocellular Carcinoma: Multidisciplinary Strategies to Provide Continuity of Care

Hepatocellular Carcinoma Management Guidelines

By
Ashraf Omar M.D,
Prof. of Hepatology & Tropical Medicine
Cairo University
Forging Partnerships in the Management of Hepatocellular Carcinoma: Multidisciplinary Strategies to Provide Continuity of Care

Staging Strategy and Treatment for Patients With HCC

HCC

- PST 0, Child-Pugh A
  - Very early stage
    - Single < 2 cm
      - Single
      - Portal pressure/bilirubin
        - Normal
        - No
      - Resection
  
- PST 0-2, Child-Pugh A-B
  - Early stage
    - Single or 3 nodules ≤ 3 cm, PST 0
      - 3 nodules ≤ 3 cm
      - Increased
      - Associated diseases
      - Yes
      - PEI/RF
  - Intermediate stage
    - Multinodular, PST 0
      - TACE
  
- PST > 2, Child-Pugh C
  - Advanced stage
    - Portal invasion, N1, M1, PST 1-2
      - Portal invasion, N1, M1
      - Yes
      - Sorafenib
  
- Terminal stage

Curative treatments

Staging Strategy and Treatment for Patients With HCC

**HCC**

- **PST 0, Child-Pugh A**
  - **Very early stage**
    - Single < 2 cm
    - Portal pressure/bilirubin Normal
  - Resection

- **PST 0-2, Child-Pugh A-B**
  - **Early stage**
    - Single or 3 nodules ≤ 3 cm, PST 0
    - 3 nodules ≤ 3 cm
    - Portal pressure/bilirubin Increased
    - Associated diseases: No
  - Liver transplant

- **PST > 2, Child-Pugh C**
  - **Intermediate stage**
    - Multinodular, PST 0
    - Portal invasion, N1, M1, PST 1-2
  - Sorafenib

  - **Advanced stage**
    - Portal invasion, N1, M1
    - No
  - TACE

  - **Terminal stage**
    - Symptomatic (unless LT)

**Surgical treatments:** applicable overall to 10% to 15% of HCC at first diagnosis and 2% to 5% of recurrent HCC

**Nonsurgical treatments:** applicable overall to 65% to 75% of HCC at first diagnosis and 50% to 70% of recurrent HCC
Approved Curative Treatments for Unresectable HCC: Percutaneous Ablation

- Local ablation: safe and effective therapy for patients who cannot undergo resection or as a bridge to transplantation (level II)

- Alcohol injection and radiofrequency are equally effective for tumors < 2 cm
  - However, necrotic effect of radiofrequency is more predictable in all tumor sizes
  - In addition, efficacy is clearly superior to that of alcohol injection in larger tumors (level I)

Approved & Investigational Noncurative Agents for Unresectable HCC

- **AASLD 2005 recommendations**
  - **Chemoembolization (TACE)** (with doxorubicin, cisplatin, or mitomycin) is recommended as first-line, noncurative therapy for nonsurgical patients with large/multifocal HCC who do not have vascular invasion or extrahepatic spread (and are not eligible for percutaneous ablation) (level I)
  
  - Tamoxifen, octreotide, antiandrogens, and hepatic artery ligation/embolization are not recommended (level I); other options such as drug-eluting beads, radiolabelled yttrium glass beads, radiolabelled lipiodol, or immunotherapy cannot be recommended as standard therapy for advanced HCC outside clinical trials

Forging Partnerships in the Management of Hepatocellular Carcinoma: Multidisciplinary Strategies to Provide Continuity of Care

Treatment of Advanced HCC (BCLC Stage C)

- AASLD 2005 recommendation: no standard therapy; patients should enroll in a randomized clinical trial[1]
- 2008 recommendation: sorafenib has become the standard of care for advanced HCC[2]
  - Prolongs OS by 3 months[3]
  - 1-year survival: 44%[4]

Intermediate/Advanced HCC: Future Directions

- 499 trials registered at clinicaltrials.gov for HCC as of August 21, 2008, including
  - Improving efficacy of RF and TACE (drug-eluting beads)
  - Exploring alternative treatments for intermediate HCC (yttrium-90)
  - Molecularly targeted agents in combination regimens (advanced HCC)
  - Molecularly targeted agents in combination with current modalities (early/intermediate HCC)
  - Improving tumor targeting of chemotherapeutic agents
  - New molecular targets and new molecularly targeted agents
Treatment of Liver Disease

- Hepatitis C: IFN + RBV
- Hepatitis B: IFN, lamivudine, adefovir, entecavir
- Alcohol: Abstinence
- Primary biliary cirrhosis: Ursodeoxycholic acid
- Hemochromatosis: Phlebotomy
- Alpha-1 ATD: None
- Nonalcoholic fatty liver: Diet and exercise
- Wilson’s disease: Zinc, trientene
- Sclerosing cholangitis: Ursodeoxycholic acid, biliary stents
- Autoimmune hepatitis: Immunosuppression
Complications of Cirrhosis

- Variceal bleeding
- Ascites/hepatorenal syndrome
- Hepatic encephalopathy
- HCC
Management of HCC

- Liver transplantation
- Resection
- Tumor ablation
  - Radiofrequency thermal ablation
  - Alcohol injection
  - Chemoembolization
- Targeted molecular therapy
- Chemotherapy
  - Regional/systemic

Potentially curative
Forging Partnerships in the Management of Hepatocellular Carcinoma: Multidisciplinary Strategies to Provide Continuity of Care

### Evidence of Benefit in Treatment of HCC

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Benefit</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Surgical treatments</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resection</td>
<td>Increased survival</td>
<td>Case series</td>
</tr>
<tr>
<td>• Adjuvant therapies</td>
<td>Uncertain</td>
<td>Randomized trial, meta-analysis, nonblinded</td>
</tr>
<tr>
<td>Liver transplantation</td>
<td>Increased survival</td>
<td>Case series</td>
</tr>
<tr>
<td>• Neoadjuvant therapies</td>
<td>Treatment response</td>
<td>Nonrandomized trials</td>
</tr>
<tr>
<td><strong>Locoregional treatment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percutaneous treatment</td>
<td>Increased survival</td>
<td>Case series</td>
</tr>
<tr>
<td>RFA vs PEI</td>
<td>Better local control</td>
<td>Randomized trial, meta-analysis, nonblinded</td>
</tr>
<tr>
<td>Chemoembolization</td>
<td>Increased survival</td>
<td>Randomized trial, meta-analysis, nonblinded</td>
</tr>
<tr>
<td>Arterial chemotherapy</td>
<td>Treatment response</td>
<td>Case series</td>
</tr>
<tr>
<td>Internal radiation</td>
<td>Treatment response</td>
<td>Case series</td>
</tr>
</tbody>
</table>

## Evidence of Benefit in Treatment of HCC (cont’d)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Benefit</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Systemic therapies</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sorafenib</td>
<td>Increased survival</td>
<td>Randomized trial, meta-analysis, double blinded</td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>No benefit</td>
<td>Randomized trial, meta-analysis, double blinded</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>No benefit</td>
<td>Randomized trial, meta-analysis, nonblinded</td>
</tr>
<tr>
<td>IFN</td>
<td>No benefit</td>
<td>Randomized trial, meta-analysis, nonblinded</td>
</tr>
</tbody>
</table>

Forging Partnerships in the Management of Hepatocellular Carcinoma: Multidisciplinary Strategies to Provide Continuity of Care

Staging Strategy and Treatment for Patients With HCC

HCC

PST 0, Child-Pugh A
- Very early stage
  - Single < 2 cm
  - Single
  - Portal pressure/bilirubin Normal
  - Resection
- Early stage
  - Single or 3 nodules ≤ 3 cm, PST 0
  - 3 nodules ≤ 3 cm
  - Increased
  - Associated diseases
  - PEI/RF

PST 0-2, Child-Pugh A-B
- Intermediate stage
  - Multinodular, PST 0
  - TACE

PST > 2, Child-Pugh C
- Advanced stage
  - Portal invasion, N1, M1, PST 1-2
  - Sorafenib
- Terminal stage
  - Portal invasion, N1, M1
  - Symptomatic (unless LT)

Curative treatments

RCTs (50%)
- Median survival: 11-20 mos

Forging Partnerships in the Management of Hepatocellular Carcinoma: Multidisciplinary Strategies to Provide Continuity of Care

Sorafenib in Advanced HCC: The SHARP Trial

- Entry criteria
  - Advanced HCC
    - Not eligible for or failed surgical or locoregional therapies
  - Child-Pugh class A disease
  - At least 1 untreated target lesion
- Exclusions
  - Previous chemotherapy
  - Previous molecularly targeted therapy

Forging Partnerships in the Management of Hepatocellular Carcinoma: Multidisciplinary Strategies to Provide Continuity of Care

**The SHARP Trial: OS and Time to Progression**

<table>
<thead>
<tr>
<th></th>
<th>Median OS</th>
<th>Placebo: 7.9 mos</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sorafenib</strong></td>
<td>10.7 mos</td>
<td></td>
</tr>
</tbody>
</table>

- **Probability of Survival**
  - **A** OS
    - Months Since Randomization
    - Probability of Survival
    - **P < .001**

- **Time to Symptomatic Progression**
  - **B**
    - Months Since Randomization
    - Probability of No Symptomatic Progression
    - **P = 0.77**

- **Time to Radiologic Progression**
  - **C**
    - Months Since Randomization
    - Probability of Radiologic Progression
    - **P < 0.001**

- **Median TTSP**
  - **Sorafenib**: 4.1 mos
  - **Placebo**: 4.9 mos

- **Median TTRP**
  - **Sorafenib**: 5.5 mos
  - **Placebo**: 2.8 mos

Strategies for Managing AEs

- Hand-foot syndrome
  - Creams and lotions
  - Avoid tight footwear
  - May require dose reduction
- Diarrhea
  - Antidiarrheal agents if severe
- Fatigue
  - Consider modafinil or methylphenidate if severe
- Hypertension
  - Start or adjust antihypertensives
Intra-arterial Locoregional Therapy

- Established
  - TACE
  - Radioembolization: yttrium-90 radioactive microspheres
- Undergoing clinical trials
  - Drug-eluting beads
Chemoembolization: Randomized Trials (Nearly Identical Techniques)

Lo et al[^1]: N = 80 with newly diagnosed unresectable HCC, 80% HBV positive, 7-cm tumors (60% multifocal)

<table>
<thead>
<tr>
<th>Technique</th>
<th>Survival, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Year 1</td>
</tr>
<tr>
<td>TACE</td>
<td>57</td>
</tr>
<tr>
<td>Supportive care</td>
<td>32</td>
</tr>
</tbody>
</table>

Llovet et al[^2]: N = 112 with unresectable HCC, 80% to 90% HCV positive, 5-cm tumors (~ 70% multifocal)

<table>
<thead>
<tr>
<th>Technique</th>
<th>Survival, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Year 1</td>
</tr>
<tr>
<td>TACE</td>
<td>82</td>
</tr>
<tr>
<td>Supportive care</td>
<td>63</td>
</tr>
</tbody>
</table>

Chemoembolization: Ineligibility Criteria

- Absolute contraindications
  - Child-Pugh class C disease
  - Poor performance status (ECOG PS > 2)
- Relative contraindication
  - Extrahepatic disease (benefit unclear)
- Former contraindication
  - PVT
    - Minimize embolization and be more selective
Conclusions

- TACE accepted as treatment of choice for unresectable (nonablatable?) HCC
- Prolonged survival established through randomized trials and prospective studies
- Best vs good performance status, Child-Pugh class A-B
- Role for yttrium-90 microspheres
- Growing role for doxorubicin-loaded beads, pending outcome of clinical trials
AASLD Guidelines: Staging Strategy and Treatment for Patients With HCC

- Very early stage: Single < 2 cm
  - Single
  - Portal pressure/bilirubin: Normal
    - Resection
  - Portal pressure/bilirubin: Increased
    - 3 nodules ≤ 3 cm
      - No
        - Liver transplant
      - Yes
        - RFA/PEI

- Early stage: Single or 3 nodules ≤ 3 cm, PST 0
  - Single
  - Associated diseases: No
    - Liver transplant
  - Associated diseases: Yes
    - RFA/PEI

- Intermediate stage: Multinodular, PST 0
  - 3 nodules ≤ 3 cm
    - No
      - Liver transplant
    - Yes
      - RFA/PEI

- Advanced stage: Portal invasion, N1, M1, PST 1-2
  - Portal invasion, PST 0, Child-Pugh A
    - Resection
  - Portal invasion, PST > 2, Child-Pugh C
    - Palliative treatments

Curative treatments:
- Resection
- Liver transplant
- RFA/PEI

Palliative treatments:
- TACE
- Sorafenib

Symptomatic
WHY LT for HCC?

LT is attractive because both the tumour as well as cirrhosis presents in 50-90% which is the fertile soil for the development of new lesions are removed by this procedure.
What should be a suitable criteria for liver transplantation for HCC?
Liver Transplantation for HCC: Milan Criteria (Stage 1 and 2)

Single tumor, not > 5 cm  
Up to 3 tumors, none > 3 cm

+ Absence of macroscopic vascular invasion, absence of extrahepatic spread

Current indications

- Single tumour < 5 cm or ≤ 3 nodules < 3 cm
- No portal thrombosis
- Overall survival
  - 1-year: 90%
  - 4-year: 75%
- Recurrence: 8%

Survival according the Milan’s Criteria on the explanted liver

P = 0.01 by the log-rank test
Can we expand the Milan criteria for hepatocellular carcinoma in liver transplantation?
UCSF Criteria

* Explant pathology: Criticised

* Clinical applicability

Total ≤ 8 cm
UCSF Criteria

Results:

- Tumors within UCSF criteria
  - 1 yr survival 90%
  - 5 yr survival 75%

- Tumors outside UCSF criteria
  - 1 yr survival 50%
  - 5 yr survival < 30%
Milan & UCSF Criteria
Radiologic Staging

Decaens et al. Liver Transpl, 2006
Beyond Milan Criteria—HCC
“Metro Ticket”

Metroticket: “Up To Seven” Criteria
Largest tumor + tumor number \( \leq 7 \)

Mazzafero, et. al. Lancet Oncol, 2009
Forging Partnerships in the Management of Hepatocellular Carcinoma: Multidisciplinary Strategies to Provide Continuity of Care

Liver transplantation for HCC

Liver transplantation for HCC: larger size, increased recurrence

Forging Partnerships in the Management of Hepatocellular Carcinoma: Multidisciplinary Strategies to Provide Continuity of Care

Milan vs “Up to 7”

Mazzafero, et. al. Lancet Oncol, 2009
Forging Partnerships in the Management of Hepatocellular Carcinoma: Multidisciplinary Strategies to Provide Continuity of Care

Transplantation for HCC

N indications

N grafts

Tumour features

Risk of recurrence

shortage

N indications

N grafts

Transplantation for HCC

Intrinsic efficacy

Waiting time
⇒ drop-out

Intent-to-transplant efficacy
Definitions

- Neoadjuvant treatment.
- Bridging
- Downstaging
• Downstaging

lowering the stage to allow for transplantation for patients who when first seen don’t qualify for LTx
Forging Partnerships in the Management of Hepatocellular Carcinoma: Multidisciplinary Strategies to Provide Continuity of Care

- Bridging

Strategy to allow patient to wait for a longer time without progression

TACE  RFA
- Neoadjuvant treatment.

Treatment before a procedure to improve outcome

- TACE
- RFA
Excellent outcome following down-staging of HCC prior to liver transplantation: an intention-to-treat analysis

Criteria for downstaging

- 1 lesion > 5 cm and up to 8 cm
- 2–3 lesions with 1 or more lesions > 3 cm and not > 5 cm, with total tumor diameter up to 8 cm
- 4–5 lesions with none > 3 cm, with total tumor diameter up to 8 cm
Excellent outcome following down-staging of HCC prior to liver transplantation: an intention-to-treat analysis

Table 4. Down-Staging Treatments Received by the 61 Patients

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No. of Patients (No. of Treatments)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laparoscopic/open RFA only*</td>
<td>11 (11)</td>
</tr>
<tr>
<td>TACE only</td>
<td>15 (34)</td>
</tr>
<tr>
<td>TACE + percutaneous ablation</td>
<td>15 (54)</td>
</tr>
<tr>
<td>TACE + percutaneous ethanol ablation</td>
<td>6 (27)</td>
</tr>
<tr>
<td>TACE + percutaneous RFA</td>
<td>9 (27)</td>
</tr>
<tr>
<td>Laparoscopic RFA + TACE</td>
<td>14 (34)</td>
</tr>
<tr>
<td>Resection†</td>
<td>6 (6)</td>
</tr>
</tbody>
</table>

*Two received open RFA, nine received laparoscopic RFA.

†One of these patients underwent resection despite a high preoperative CTP score of 11. This patient had a 5.3-cm lesion very close to the liver surface at risk for rupture. The other five patients had a CTP score of ≤7 before resection.
Forging Partnerships in the Management of Hepatocellular Carcinoma: Multidisciplinary Strategies to Provide Continuity of Care

N indications
N grafts

Tumour features
Risk of recurrence

Transplantation for HCC

Intrinsic efficacy

Waiting time
⇒ drop-out

Intent-to-transplant efficacy

shortage
Forging Partnerships in the Management of Hepatocellular Carcinoma: Multidisciplinary Strategies to Provide Continuity of Care

Living donor transplantation and HCC

Transplantation indication for HCC

- Tumour features
- Risk of recurrence

Intrinsic efficacy

Waiting time
⇒ drop out

intent to transplant efficacy

shortage
Is LDLT for HCC as efficacious as DDLT?
Is LDLT for HCC as efficacious as DDLT?

**PRO**


**CON**


Is LDLT for HCC as efficacious as DDLT?

Graft survival in HCC

- Living: 277
- Cadaveric: 7236

Total Log Rank test p = 0.11
Is LDLT for HCC as efficacious as DDLT?

Patients survival in HCC

Living: 276
Cadaveric: 6685

Total Log Rank test p = 0.12
Predictors of Recurrence after LT

1. L.N involvement
2. gross vascular invasion (angio / CT)
3. microscopic invasion (in the specimen)
4. > 5cm
5. multiple lesions
6. infiltrating rather than circumscribed lesion
7. More than one lobe
8. pTNM staging
How to Minimize Risk of Recurrence?

- HCC biology
- Refinement of immunosuppression: “mTOR”?
- Radiologic identification of VI
- Prospective multicenter RCT: is the key.
Conclusion

- HCC patients exceeding Milan criteria can still be cured; nodules 5-7cm and with no gross vascular invasion >> good survival & higher recurrence rate.

- HCC is a prime indication for LDLT ...>.lower dropout, extending the acceptance of HCC for LT without waiting for cadaveric LT.

- However is no consensus on the use of LDLT for HCC due to lack of adequate data