Staging and Treatment of HCC in the Era of LDLT: a referring physician’s view

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Multidisplinary Approach to the Management of HCC

- **Surgeon**: resection, transplantation
- **Liver Pathologist**: tissue diagnosis
- **Hepatologist**: primary physician
- **Diagnostic Radiologist**: imaging diagnosis
- **Interventional Radiologist**: TACE, RFA
- **Radiation Oncologist**: radiation therapy
Management of HCC
(Medical Practice: Science + Art)

vs

Playing Golf
(Golf Tournament: Science + Art)
The Purposes of Tumor Staging

• Aid the clinician in planning treatment
• Give some indication of prognosis
• Assist in evaluating the results of treatment
• Facilitate the exchange of information between treatment centers

Uniqueness and Difficulties in Developing HCC Staging System

- Tumor: not a single predominant cause of death
- Not only anatomical stage, but also functional stage
  - Treatment modalities affect functional stage.

- No standard treatment strategy
- Proper staging system is varying according to treatment modalities.
HCC Staging Systems

- AJCC/UICC
- Okuda staging
- French score system
- German score system
- BCLC staging
- CLIP score
- JIS staging
- CUPI staging

Llovet JM, et al. Semin Liver Dis 1999
CLIP Investigators. Hepatology 2000
<table>
<thead>
<tr>
<th>Time</th>
<th>Section</th>
<th>Chairperson</th>
</tr>
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<tbody>
<tr>
<td>09:00-10:20</td>
<td>Symposium 2: Staging of HCC: Which System Should We Use?</td>
<td><strong>Main Hall</strong></td>
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<tr>
<td>09:00-09:20</td>
<td>BCLC</td>
<td>Masatoshi Makuchib, Japan / Hyo-Suk Lee, Korea</td>
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<tr>
<td>09:20-09:40</td>
<td>AJCC/UICC</td>
<td>Jean-Nicolas Vauthey, USA</td>
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<tr>
<td>09:40-10:00</td>
<td>Okuda, Tokyo and JIS Scores</td>
<td>Masao Omata, Japan</td>
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<tr>
<td>10:00-10:20</td>
<td>Panel Discussion</td>
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BCLC Staging: strategy for staging and treatment assignment

Clinical Management of Hepatocellular Carcinoma. Conclusions of the Barcelona-2000 EASL Conference

AASLD PRACTICE GUIDELINE

Management of Hepatocellular Carcinoma

Simplified Staging for Hepatocellular Carcinoma

A modified Japan Integrated Stage score for prognostic assessment in patients with hepatocellular carcinoma

Ikai I, Kenichi Takayasu, Masao Omata, Kiwamu Okita, Yasuni Nakanuma, Yutaka Matsuyama, Masatoshi Makuuchi, Masamichi Kojirō, Takafumi Ichida, Shigeki Arii, and Yoshio Yamaoka for the Liver Cancer Study Group of Japan
Jordi Bruix

Jean-Nicolas Vauthey
HCC Treatment Guidelines: EASL and AASLD

To maximize the validity of guidelines

Adapted for a local setting

HCC Treatment in Korea: Current Issues and Future Directions
Development of Staging System in Korea

Establishment of staging system

Standard treatment based on the staging system

Survival rates according to staging system
Development of Staging System in Korea

Establishment of staging system

Standard treatment based on the staging system

Survival rates according to staging system
Development of Staging System based on Natural History of HCC’s in Korea

1,184 patients with new HCC

127 patients untreated at SNUH

17 patients - treated in other hospital or uncertain treatment history
30 patients - Child-Pugh class C

80 untreated patients
Multivariable analysis after adjustment for Child-Pugh score

Median survival (range)
- T1: 13.2 mo (0.6-42.5)
- T2:  8.3 mo (0.8-26.8)
- T3:  1.9 mo (0.1-49.3)
- T4:  1.0 mo (0.2-1.5)
Independent Risk Factors: N Stage and M Stage

- Multivariable analysis after adjustment for T stage and Child-Pugh score

Survival

Follow-up duration (months)

Survival

Follow-up duration (months)

N stage

M stage

P = 0.218

P = 0.157
Comparison of Natural History and Respective Staging System: 

TNM Staging

No discrimination ability between stage II and IV ($P>0.05$)
Comparison of Natural History and Respective Staging System: 
Okuda Staging

No discrimination ability between stage II and III ($P=0.909$)

I ($n=23$)

II ($n=46$)

III ($n=11$)

Survival

Follow-up duration (months)

$P=0.007$
Comparison of Natural History and Respective Staging System: BCLC Staging

No discrimination ability between stage C and D ($P=0.171$)
No discrimination ability between score 2, 3, 4 and 5 ($P > 0.05$)
Comparison of Natural History and Respective Staging Systems

• **Independent prognostic factors for untreated HCC**
  - Intrahepatic tumor stage: T stage, BCLC
  - Liver function: Child-Pugh score

• **Node (N stage) and distant metastasis (M stage)**
  - Failed to show statistical significance

• **Discrimination ability of other staging systems**
  - may be confounded by treatment result
BCLC Staging: strategy for staging and treatment assignment

- according to the extent of disease and the predicted prognosis
- stratify patients into treatment groups
Comparison of Organ Donation Rates from Deceased Donors in Different Countries

<table>
<thead>
<tr>
<th>Country</th>
<th>Number of Deceased Donors per Million of Population</th>
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</thead>
<tbody>
<tr>
<td>Japan</td>
<td>0.07</td>
</tr>
<tr>
<td>Korea</td>
<td>1.9</td>
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<tr>
<td>Hong Kong</td>
<td>4.2</td>
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<tr>
<td>Singapore</td>
<td>4.7</td>
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<tr>
<td>Taiwan</td>
<td>6.6</td>
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<tr>
<td>Australia</td>
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<td>United Kingdom</td>
<td>10.7</td>
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<tr>
<td>Canada</td>
<td>12.8</td>
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<td>Germany</td>
<td>14.4</td>
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<td>Portugal</td>
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<td>Italy</td>
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<td>France</td>
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<td>USA</td>
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<td>Spain</td>
<td>35.1</td>
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</table>

De Villa et al. Oncologist. 2007;12:1321-31
Annual Overall Number of Deceased and Living Donor Liver Transplants in Asia (Excluding Mainland China)

De Villa et al. Oncologist. 2007;12:1321-31
Annual Proportion and Number of Liver Transplants for HCC in Asia (Excluding Mainland China)

De Villa et al. Oncologist. 2007;12:1321-31
Revision of Staging System

Establishment of staging system

Standard treatment based on the staging system

Survival rates according to staging system

Introduction of new treatments (LDLT, Sorafenib)
Critical Appraisal of Indications for DDLT vs LDLT in the Management of HCC: a referring physician’s view
5-Year Survival-based Deceased Donor Liver Allocation: Utility Justice

To outweigh the harm caused to other patients on waiting list

5-Year Survival-based Deceased Donor Liver Allocation: Utility Justice

To outweigh the harm caused to other patients on waiting list

Volk ML et al. Am J Transplant 2008;8:839
Selection Criteria for HCC with DDLT: Milan Criteria

- Expanded Criteria
  - 5-yr survival rate
- Milan Criteria
  - Organ availability
Selection Criteria for HCC with DDLT: Milan Criteria

- Expanded Criteria
- Milan Criteria

Organ availability

5-yr survival rate
Selection Criteria for HCC with DDLT: Milan Criteria
Selection Criteria for HCC with LDLT: recipient survival benefit-based

Milan Criteria

Expanded Criteria

Potential harm (donor)

Expected benefit (recipient)

Lee HS. Dig Dis 2007;25:296
Selection Criteria for HCC with LDLT: recipient survival benefit-based

Milan Criteria

Expanded Criteria

Expected benefit (recipient)

Potential harm (donor)

Lee HS. Dig Dis 2007;25:296
Selection Criteria for HCC with LDLT: recipient survival benefit-based

Milan Criteria

Expanded Criteria

Potential harm (donor)

Expected benefit (recipient)

Lee HS. Dig Dis 2007;25:296
Survival Benefit-based Indication for LDLT: early stage

- Hypothetical survival curves of HCC

A. HCC within Milan criteria, LDLT (75%)
B. HCC within Milan criteria, non-OLT (50%)
C. Single HCC, surgical resection

Lee HS et al. J Clin Oncol 2002;20:4459
Survival Benefit-based Indication for LDLT: early stage

- Hypothetical survival curves of HCC

A. HCC within Milan criteria, LDLT
B. HCC within Milan criteria, non-OLT
C. Single HCC, surgical resection

Lee HS et al. J Clin Oncol 2002;20:4459
Survival Benefit-based Indication for LDLT: intermediate stage

• Hypothetical survival curves of HCC

A. HCC beyond Milan criteria, non-OLT

B. HCC beyond Milan criteria, LDLT

Lee SG et al. Liver Transplant 2008;14:935
Lee HS et al. J Clin Oncol 2002;20:4459
Survival Benefit-based Indication for LDLT: advanced stage

- Hypothetical survival curves of HCC

A. HCC, beyond Milan, best supportive care
B. HCC, within Milan, treated with LDLT
C. HCC, beyond Milan, treated with LDLT
Survival Benefit-based Indication for LDLT

- Early
- Intermediate
- Advanced
BCLC Staging Classification and Treatment Strategies

Llovet JM et al. J Natl Cancer Inst 2008;100:698
Revision of Staging System

Establishment of staging system

Standard treatment based on the staging system

Survival rates according to staging system

Introduction of new treatments (LDLT, Sorafenib)
Cellular Targets of Sorafenib, a Multikinase Inhibitor

[Diagram showing the cellular targets and mechanisms of Sorafenib, including VEGF, PDGFB, SCF, GDNF, VEGFR, PDGFR, c-Kit, RET, Receptor autophosphorylation, Activation of Raf, Cell survival (anti-apoptotic effects), Neovascularization, MEK/ERK, Invasion and metastasis, Tumour cell proliferation.]
The Mad Science

12  Do test results really prove that I’ll hit the ball significantly farther and straighter with newer golf clubs?

On moving past golf industry hype and learning to play better golf

Philip Moore

Contents

Forward

i  Why I wrote this little book

Introduction

iii  It’s time to see things differently

QUESTIONS you should be asking about

14  Is the modern equipment the primary reason today’s professional golfers hit the ball farther and score lower?

17  How come touring professionals are scoring lower, but the average golfer isn’t?

19  Are the newest golf clubs always more forgiving and easier to play with?

20  Are the irons I hit the farthest the best irons for me?

22  How much better would I play with an expensive set of brand name irons?

23  What irons should I be using?
Sorafenib in Advanced Hepatocellular Carcinoma

A. Overall Survival

- Probability of Survival
- Months since Randomization
- Sorafenib and Placebo (P < 0.001)

B. Time to Symptomatic Progression

- Probability of No Symptomatic Progression
- Months since Randomization
- Sorafenib and Placebo (P = 0.77)

C. Symptomatic Progression-Free Probability

- Number at Risk
- Months


Contents

Forward

i  Why I wrote this little book

Introduction

iii  It’s time to see things differently

QUESTIONS you should be asking about YOUR GOLF CLUBS

3  Is the modern golf club a high-tech piece of equipment?

5  Why are brand name golf clubs so expensive?

7  Can anything else that really matters be done to a golf club?

9  How much better are golf clubs really getting every year?

12  Do test results really prove that I’ll hit the ball significantly farther and straighter with newer golf clubs?

14  Is the modern equipment the primary reason today’s professional golfers hit the ball farther and more squarely?

22  How much better would I play with an expensive set of brand name irons?
**BCLC Staging Classification and Treatment Strategies**

**Stage 0**
- PST 0, Child-Pugh A

**Stage A-C**
- PST 0-2, Child-Pugh A-B

**Stage D**
- PST >2, Child-Pugh C

**Very early stage (0)**
- Single ≤ 2cm.
- Carcinoma in situ

**Early stage (A)**
- Single or 3 nodules < 3cm, PS 0

**Intermediate stage (B)**
- Multinodular, PST 0

**Advanced stage (C)**
- Portal invasion, N1, M1, PST 1-2

**End stage (D)**
- Single
- Portal pressure/ bilirubin
- Normal
- Increased

**Associated diseases**
- Yes
- No

**Resection**
- Liver Transplantation (CLT / LDLT)
- PEI / RF
- TACE
- Sorafenib

**Curative Treatments (30%)**
- 5-yr survival: 40-70%

**Randomized controlled trials (50%)**
- Median survival 11-20mo

**Symptomatic (20%)**
- Survival < 3mo

Prospective, randomized, double-blind, multi-center, Phase III clinical study on transarterial chemoembolization (TACE) combined with Sorafenib® versus TACE plus placebo in patients with hepatocellular cancer before liver transplantation – HeiLivCa [ISRCTN24081794]

Hoffmann K et al. BMC Cancer 2008;8:349
GOLF

HOW GOOD
DO YOU WANT TO BE?

Bill Kroen, Ph.D.
Author of the Best-selling Golf Tip-a-Day Calendar
Summary: Staging and Treatment of HCC in the Era of LDLT

HCC’s

Child-Pugh A
- Single HCC >5 cm
  - PV invasion
    - No: Resection
    - Yes: Resection

Child-Pugh A-B
- <3 cm, No. <3
- HCC No. >3
  - PV invasion
    - No: TACE
    - Yes: LDLT

Child-Pugh C
- Beyond Milan
  - PV invasion
    - No: LDLT
    - Yes: BSC
- Within Milan
  - PV invasion
    - No: LDLT
    - Yes: DDLT/LDLT

Recurrence
Summary: Staging and Treatment of HCC in the Era of LDLT

HCC’s

Child-Pugh A
- Single HCC >5 cm
  - PV invasion
    - No: Resection
    - Yes: Further treatment depending on invasion

Child-Pugh A-B
- <3 cm, No. <3
  - PV invasion
    - No: Resection
    - Yes: Further treatment depending on invasion

Child-Pugh C
- HCC No. >3
  - Beyond Milan
    - PV invasion
      - No: LDLT
      - Yes: TACE
  - Within Milan
    - PV invasion
      - No: LDLT
      - Yes: BSC
      - No: DDLT/LDLT

Recurrence
**Down Staging vs Salvage Liver Transplantation**

**Down staging**
- **HCC beyond Milan Criteria**
  - Loco-regional therapy (LRT) or TACE
    - Responsive to LRT or TACE
      - Selection of less aggressive HCC
        - Progressive disease
          - Down staging
            - Liver transplantation
              - Favorable survival
        - Liver transplantation
          - Favorable survival
    - Progressive disease
      - Down staging
        - Liver transplantation
          - Favorable survival

**Salvage LT**
- **HCC within Milan Criteria**
  - Surgical resection of LRT
    - recurrence (-) Liver transplantation
    - recurrence (+) Worse prognosis (?)
  - less responsive to SR or LRT
    - Selection of more aggressive HCC
## Conclusion: Indications of Liver Transplantation for HCC

<table>
<thead>
<tr>
<th></th>
<th>DDLT</th>
<th>vs</th>
<th>LDLT</th>
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<tr>
<td><strong>Donor liver allocation</strong></td>
<td><strong>5-year survival based</strong></td>
<td>vs</td>
<td><strong>Survival benefit based</strong></td>
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<td><strong>Down staging</strong></td>
<td>+++</td>
<td>vs</td>
<td>+</td>
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<tr>
<td><strong>Salvage LT</strong></td>
<td>--</td>
<td>vs</td>
<td>+++</td>
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<td><strong>Urgency</strong></td>
<td>MELD</td>
<td>vs</td>
<td>Child-Pugh score</td>
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The Complete Idiot's Guide to Golf helps you build the skills you need to become a consistent, more successful golfer.

Michelle McGann, six-time winner on the LPGA tour, gives you:

- Idiot-proof steps for building a great golf swing
- Valuable tips and drills that make practice pay off
- Quick and easy ways to shave strokes off your score

Michelle McGann with Matthew Rudy

Michelle McGann has played on the Ladies Professional Golf Association tour for nine years. In 1996, she won three titles—the Oldsmobile Classic, the Youngstown-Warren LPGA Classic, and the State Farm Rail Classic—and finished eighth on the LPGA money list with $498,561.

Matthew Rudy has been a golf reporter at Sports Illustrated since 1995. Rudy has covered major events such as the U.S. Open, the Masters, and the Ryder Cup, as well as numerous LPGA events.

Michelle McGann shares her best tips and techniques in more than 100 photos inside!