HCC treatment in China

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Incidence of hepatocellular carcinoma (HCC) in the world
In 2008, China’s new HCC cases totaled 410,000, accounted for 54% of total global incidence; death toll is about 385,000, ranking No. 2 of cancer mortality.

China is the top HCC case.
Risk factors for HCC in China

- **Virus infections**
  - 70% HCC are associated with HBV infection
  - Infection rate 7% (93 million)

- **Alcoholic liver disease**

- **Others** (Environmental factors such as aflatoxin in food)
Radiological diagnosis of HCC

- MRI LAVA sequence fully demonstrate the characteristics of the enhanced lesion

- Bordline Dysplastic nodules

- Hepatic artery supply

- PV supply

- HCC

- T1, T2 phase high, low signal enhanced, mass
Curative treatment for HCC

- Liver transplantation
- Hepatectomy
- Ablation
Liver and kidney transplantations in Peking University Transplantation Center

Total: Kidney transplantation  2,015    Liver transplantation  996 ( HCC 50% )
Liver transplantation in China

Total: 23,129
Tumor distribution in LTx recipients

- HCC with symptoms, 5,882 (28.25%)
- HCC without symptom, 1,953 (9.38%)
- HCC recurrence after resection, 1,074 (5.16%)
- Accidental HCC, 211 (1.01%)
- Combined HCC and cholangiocarcinoma, 424 (2.04%)
- Other benign liver tumor, 16 (0.08%)
- Other malignant liver tumor, 409 (1.96%)
- No tumor, 10,474 (50.32%)
HCC distribution according to Milan criteria

<table>
<thead>
<tr>
<th>Year</th>
<th>Percentage within Milan: 2,763</th>
<th>Percentage outside Milan: 5,142</th>
</tr>
</thead>
<tbody>
<tr>
<td>1993</td>
<td>1</td>
<td>1</td>
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<tr>
<td>1995</td>
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<tr>
<td>1998</td>
<td>3</td>
<td>12</td>
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<td>1999</td>
<td>11</td>
<td>44</td>
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<td>2000</td>
<td>63</td>
<td>29</td>
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<td>2001</td>
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<td>2002</td>
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<td>2003</td>
<td>626</td>
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<td>2004</td>
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<td>2005</td>
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<td>390</td>
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<td>2006</td>
<td>399</td>
<td>250</td>
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<tr>
<td>2007</td>
<td>553</td>
<td>321</td>
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<tr>
<td>2008</td>
<td>547</td>
<td>299</td>
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<tr>
<td>2009</td>
<td>607</td>
<td>334</td>
</tr>
<tr>
<td>2010</td>
<td>420</td>
<td>253</td>
</tr>
<tr>
<td>2011</td>
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</tbody>
</table>
Overall recipient survival rate of LT patients

HCC vs. Non-HCC

1980-2011

N = 16851

Log Rank $P < .001$

Comparatively
Cumulative recipient survival rates by year 1993-2010

- Total: 7,101
- Log-rank $P < 0.001$

*Survival rates computed based on transplant cohorts for whom follow-up data were available.*
The SRs of LDLT cases for HCC is significantly better than DDLT. The reasons:
1. LDLT cases are far fewer than DDLT
2. LDLTs have a short graft ischemia time
3. We performed most LDLT in recent years
Recurrence rate for HCC recipients

N = 8816

Cumulative Recurrence Rate (%) vs. Survival Time (months)

- 19.28% at 0 months
- 29.53% at 18 months
- 33.69% at 36 months

Total follow-up period: 150 months
Milan Criteria
- solitary tumor ≤5 cm
- or three or fewer lesions with the largest lesion ≤3 cm
- without macrovascular invasion, lymph node involvement and distant metastasis

FUDAN Criteria
- solitary lesions ≤9 cm in diameter
- or no more than 3 lesions, the largest ≤5 cm with a total tumor diameter ≤9 cm
- without macrovascular invasion, lymph node involvement and distant metastasis

UCSF Criteria
- solitary tumor ≤6.5 cm
- or three or fewer nodules with the largest lesion ≤4.5 cm and total tumor diameter ≤8 cm
- without macrovascular invasion, lymph node involvement and distant metastasis

Hangzhou Criteria
- total tumor diameter less than or equal to 8 cm
- if total tumor diameter is more than 8 cm, must have preoperative AFP level less than or equal to 400 ng/mL, simultaneously
Survival analysis for a variety of selection criteria

|                | No.  | Cumulative survival(%) |  |  |  |
|----------------|------|------------------------|  |  |  |
|                | 1-year | 3-year | 5-year |  |
| Milan\(^{-1}\) | 4366   | 69.7      | 44      | 34.8  |
| Milan\(^{+1}\) | 2284   | 85.8      | 75.4    | 71.1  |
| UCSF\(^{-2}\) | 3753   | 67.7      | 40.4    | 30.9  |
| UCSF\(^{+2}\) | 2584   | 85.6      | 74.7    | 70.1  |
| Fudan\(^{-3}\) | 3499   | 66.7      | 39.2    | 29.8  |
| Fudan\(^{+3}\) | 2853   | 85.4      | 73.5    | 68.5  |
| Hangzhou\(^{-4}\) | 2794   | 63.3      | 34      | 24.9  |
| Hangzhou\(^{+4}\) | 4699   | 83.6      | 69.3    | 63.6  |

* The number of cohorts for the five criteria differs based on data availability

* Milan IN: within Milan criteria; Milan OUT: beyond Milan criteria; other criteria applied.
Survival comparison of expanded criteria to Milan criteria

<table>
<thead>
<tr>
<th></th>
<th>Milan(^1) &amp; Milan(^2)</th>
<th>UCSF(^1) &amp; Milan(^2)</th>
<th>Fudan(^1) &amp; Milan(^-)</th>
<th>Hangzhou(^1) &amp; Milan(^-)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No.</strong></td>
<td>2253</td>
<td>331</td>
<td>569</td>
<td>1163</td>
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<tr>
<td><strong>New patients (%)(^3)</strong></td>
<td>12.81</td>
<td>22.02</td>
<td>34.05</td>
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</table>

<table>
<thead>
<tr>
<th>Survival rate (%)</th>
<th>Milan(^1) &amp; Milan(^2)</th>
<th>UCSF(^1) &amp; Milan(^2)</th>
<th>Fudan(^1) &amp; Milan(^-)</th>
<th>Hangzhou(^1) &amp; Milan(^-)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-year</td>
<td>85.9</td>
<td>84.1</td>
<td>84.1</td>
<td>84.0</td>
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<tr>
<td>2-year</td>
<td>75.5</td>
<td>69.6</td>
<td>65.3</td>
<td>66.4</td>
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<tr>
<td>3-year</td>
<td>71.2</td>
<td>62.5</td>
<td>56.7</td>
<td>57.2</td>
</tr>
<tr>
<td><strong>P(^4)</strong></td>
<td>.069</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td></td>
</tr>
</tbody>
</table>

1. Cases within Milan criteria/Fudan criteria/Hangzhou criteria.
2. Cases beyond Milan criteria.
3. Proportion of patients increased based upon the expand criteria.
After 06, LTx cases↓. The following years, LDLT↑. LDLT ratio was the highest in 2007, when it was around 24%
Living donor liver transplantation in Peking University People’s Hospital

- 21 cases 2003.2—2010.12
- 15 cases Adult-adult LDLT
- 6 cases Pediatric LDLT
Annual distribution of LTx in China

2009-2013/7

N= 9367

<table>
<thead>
<tr>
<th>Year</th>
<th>LDLT %</th>
<th>DCD %</th>
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<tbody>
<tr>
<td>2009</td>
<td>0.72%</td>
<td></td>
</tr>
<tr>
<td>2010</td>
<td>1.38%</td>
<td></td>
</tr>
<tr>
<td>2011</td>
<td>4.79%</td>
<td></td>
</tr>
<tr>
<td>2012</td>
<td>15.37%</td>
<td></td>
</tr>
<tr>
<td>2013</td>
<td>25.49%</td>
<td></td>
</tr>
</tbody>
</table>

N= 9367

Data source time July 2013

*Data source time July 2013
Hepatectomy for HCC

- Surgical mortality rate <1%
- Postoperative liver function failure is not acceptable
Evolution of hepatectomy concept

1887-1940s
Aimless hepatectomy

1940-1960s
Regular hepatic lobectomy

1960-1980s
Irregular hepatectomy

1980s-2000
Anatomical segmentectomy

2000----
Precise hepatectomy

development period is present here
Evaluation of Liver Function

- Precise evaluation in preoperation and intraoperation hepatic functional reserve assessment (ICG), 3D imaging, virtual surgery, Intraoperative Ultrasound (IOUS)

ICG Injection → Combined with protein → Absorbed by hepatocyte → Excreted through bile

Liver Function and Hepatectomy Procedure

- **Ascites**
  - Without or Controllable
    - Total Bilirubin Value
      - Normal
        - ICG15'
          - Normal
            - Rt. Lobectomy
            - Trisegmentectomy
          - K=0.15
            - 10~19%
              - Rt. ANT. Seg.
              - Lt. Lobectomy
              - Cent. Bisegmentectomy
              - S VIII + S VII
              - S V + S VI
      - 1.1~1.5mg/dl
        - Limited Resection
          - K=0.11
          - 20~29%
            - Subsegmentectomy
            - Couinaud's One Seg.
        - 1.6~1.9mg/dl
          - Enucleation
            - K=0.08
            - 30~39%
              - Limited Resection
            - 2.0mg/dl ≤
              - No Indication for Hepatectomy

- Incontrollable
  - No Indication for Hepatectomy
3D image evaluation and surgical plan

Female, 63 years old, Caudate lobe HCC, Child A, ICGR15 < 10%
Hepatectomy technologies

- Hepatic inflow occlusion, parenchyma transection (CUSA, helix Hydro-Jet) vascular resection and reconstruction

- Transect liver parenchyma and vascular simultaneously
- ≤ 3mm pipe can be safely cut
- Suitable for liver surrounding area, but hemostatic effect is not good to liver parenchyma
- Ultrasonic-Harmonic Scalpel
 Operative Procedure of Systematic Subsegmentectomy

- Staining of Subsegment Marking with Electric Cautery
- Tattooing of Parenchyma
- Hemihepatic Blood Occlusion
- Division of Parenchyma
- Raw Surface after Segmentectomy


Dye inject PV into tumor, decide how much size...
Reconstruction of right hepatic vein
Reconstruction of middle hepatic vein
One study: experience of hepatectomy in single center (1989-2008, n=1198)
Overall survival

Tumor–free survival

One study: experience of hepatectomy in China
(1989-2008, n=1198)
One case study: Twenty years of hepatectomy experience in China single center


5-year survival 46.3%
10-year survival 25.4%
Laparoscopic resection of Segment Ⅶ and Ⅶ.
daVinci robotic hepatectomy
Local ablation treatment of HCC
Male, 48 y, HCC after TACE, AFP 1200

• Before RFA, Enhanced CT shows tumor activity
• One year after RFA, CT shows the tumor shrinks with no activity
• Survive beyond 3 years status
Peking University Research Institute for Liver Cancer
HCC RFA survival rate (2007.1-2010.5, n=172)

<table>
<thead>
<tr>
<th>Tumor size (cm)</th>
<th>1 year</th>
<th>3 year</th>
<th>5 year</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.5~5.0</td>
<td>79.8</td>
<td>57.5</td>
<td>46.5</td>
</tr>
<tr>
<td>5.1~7.0</td>
<td>81.3</td>
<td>43.9</td>
<td>25.4</td>
</tr>
<tr>
<td>Total</td>
<td>80.4</td>
<td>52.0</td>
<td>37.5</td>
</tr>
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HCC biological targeted therapy

1. Sorafenib-HCC metastasis and recurrence prevention - global multi-center clinical trials
   - Sorafenib + Erlotinib (SEARCH)
   - Radical treatment (resection, RFA) + sorafenib (STORM)

2. Sunitinib, Erlotinib, Gefitinib, Lapatinib, Avastin
Other treatments of HCC

- Chemotherapy: (FOLFOX4)
- TACE (transcatheter arterial chemoembolization)
- Gene therapy (p53)
- Biotherapy (thymosin α1)
- Radiotherapy
- Others
Comprehensive treatments maximize survival rates of HCC patients

Local treatment
- Radical/reduce tumor load
- Resection/LTx
- Ablation/TACE

Systematic therapy
- Inhibit tumor/reduce recurrence
- Sorafenib

Treatment of concomitant diseases
- Improve HCC prognosis/reduce recurrence
- Antivirus treatment

In summary
Basic research

- **HCC biomarker**
  Cancer/Testis antigen
  - MAGE-1 73.5%  
  - SSX-1 73.5%
  - CTP-11 67.6%, at least one 94.1%

- **Microenvironment and HCC metastasis**
  Immune cells (Treg, Th1, Th2, CD8+ T cell, MDSC)

- **HCC stem cell (Self-renewal, Constant proliferation)**
  Side population cells/CD133/CD90/CD24
  Development, show promise
Potential Collaboration

• Large number HCC patients (most of them are HBV related)

• Large number liver resection specimen (Bio-bank)
Thank you for your attention!
## New HCC cases and death cases (2008)

<table>
<thead>
<tr>
<th></th>
<th>World</th>
<th>China</th>
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<tbody>
<tr>
<td><strong>Male</strong></td>
<td><strong>Female</strong></td>
<td><strong>Male</strong></td>
</tr>
<tr>
<td>New cases</td>
<td>523,000</td>
<td>293,000</td>
</tr>
<tr>
<td>Death cases</td>
<td>477,000</td>
<td>267,000</td>
</tr>
</tbody>
</table>
Systematic Subsegmentectomy
/anatomical segmental hepatectomy

The latest ultrasonic probe
CUS A and Hydro Jet Dissector

- Selective smash liver parenchyma
- Accurately reveal intrahepatic duct structure
- Benefit for hilar anatomy and important intrahepatic pipeline
- Relatively slow, more expensive
70 y, male, CT shows 4 cm recurrence HCC
Habib Radiofrequency ablation of liver resection
Multidisciplinary treatment model (MDT) of HCC

Performance Status

Liver function

extrahepatic metastasis

Vascular invasion

Tumor number

Tumor size

extrahepatic metastasis

Liver function

Vascular invasion

Tumor number

Tumor size

Tumor number

Tumor size

Treatment

- Resection
- Ablation ≤ 3 cm
- LTx

- Resection
- TACE + Ablation
- LTx

- TACE
- Resection
- Radiotherapy
- Targeted Therapy
- chemotherapy

- TACE
- Resection
- Radiotherapy
- Targeted Therapy
- chemotherapy

- TACE
- Resection
- Radiotherapy
- Targeted Therapy
- chemotherapy

- Supportive treatment
- LTx

- Supportive treatment
MRI manifestations of HCC (普美显) (Gadoxetate Disodium, Gd-EOB-DTPA)

Lesion shows T1 slightly low signal (A) T2 slightly high signal (A), clear boundary, visible pseudocapsule sign. Mass is significantly heterogeneously enhanced in arterial phase (C), portal venous phase (D) and equilibrium phase (E) show low signal, hepatobiliary phase (F) shows significantly low signal. Hepatobiliary phase (F) surrounding liver parenchyma signal improves significantly.