State Of the Art 2014
Hepatocellular Carcinoma

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2nd Asia Pacific Symposium on
Liver Directed Y-90 Microsphere Therapy
1st Nov 2014, Singapore
Rapid Evolution in the Management of HCC

• The last decade has seen better approaches and more efficacious therapies for HCC e.g.
  – Better survival with improved surgical approaches
  – Selective internal radiation therapy with ytium-90
  – Radio-frequency and microwave ablation
  – New systemic therapies

• The rapid evolution has lead to significant improvement in clinical outcomes

• New clinical trial data will lead to additional changes in management over the next few years
State of the Art 2014

an evolution

1. The Diagnosis of HCC
   • The AASLD criteria, gadoxcetic acid

2. Management in Early HCC
   • Resection, transplantation, RFA

3. Management in Intermediate HCC
   • Loco-regional therapy, resection, transplantation

4. Management in Metastatic HCC
   • Systemic therapy
Current Diagnosis of HCC: AASLD 2010

Based on multi-phasic imaging
But this cannot diagnose HCC that is < 1 cm or non-enhancing/non-washout

However early diagnosis = better survival
### WORK UP FOR DIAGNOSIS - HEPATOCELLULAR CANCER (HCC)

<table>
<thead>
<tr>
<th>Clinical Presentation and Liver Nodule Size</th>
<th>Imaging</th>
<th>Biopsy</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1 cm</td>
<td>Repeat Ultrasound at 3mo – 6mo [2,3] (level – 1a)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 1 cm</td>
<td>4 – phase MDCT/dynamic contrast enhanced MRI [3] (level – 1b)</td>
<td>Arterial hypervascularity AND venous or delayed phase washout on the background of a cirrhotic liver [2,4] (level -1b)</td>
<td>Ye</td>
</tr>
<tr>
<td>Elevated AFP in a patient with chronic HBV/HCV and/or cirrhosis [1,2] (level 1a)</td>
<td>Repeat Ultrasound at 3mo (or see 1mo) [2] (level – 1b)</td>
<td>Investigate according to size character</td>
<td>No</td>
</tr>
</tbody>
</table>

**Other Considerations for Diagnosing HCC**

1. For suspicious lesions that do not fulfil the AASLD requirements for diagnosis by imaging, biological imaging with gadoxetic acid (PrimovistTM) may be utilized for diagnosis of HCC according to the 2011 international consensus statement [8,11] (level – 1b):

   “Lesions without arterial phase hyper-enhancement but with both venous phase hypo-enhancement and hepatobiliary phase hypo-intensity at gadoxetic acid–enhanced MRI have a high likelihood of being high-grade dysplastic nodules or well-differentiated HCCs and should be considered “high-risk” lesions”

2. In selected cases, a patient with risk factors for HCC such as chronic viral hepatitis, liver cirrhosis etc. may be diagnosed with HCC namely:
   - **Space occupying lesion of the liver demonstrated by CT scan (non-dynamic) or MRI (non-dynamic) AND Serum alpha-feto protein level of at least 400 mcg/L [12,13] (level – 2b)**

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**Oxford Centre for Evidence Based Medicine: Levels of Evidence.**

**National Cancer Center Singapore Consensus Guidelines on Liver Cancer**

http://www.ncs.com.sg/PatientCare/ComprehensiveLiverCancerClinicDocuments/CLCC guideline Final Ver to upload PDF 26092014.pdf
Use of biological radiological contrast agents

Gadoxetic acid Enhanced MRI Liver: Dynamic and Hepatocyte-Specific Phase

- Gadoxetic-acid accumulates in functioning hepatocytes and leads to marked signal enhancement in hepatic tissue
- Hepatic lesions without functioning hepatocytes do not take up Gadoxetic-acid and appear dark in the hepatobiliary phase compared to the bright hepatic tissue
What determines survival in HCC?

1. The *Stage of the Cancer*

2. The *Underlying Function of the liver*

3. The *General Health of the patient*

4. Appropriate *Treatment* the patient receives
Stages of Liver Cancer

Early Stage HCC
- Lesions within the Milan Criteria
  - criteria:
    - Solitary tumour $\leq 5\text{cm}$ OR $\leq 3$ tumours, each $< 3\text{cm}$ AND No invasion of blood vessels and no distant spread

Locally Advanced HCC
- Lesions confined to the liver that are outside of the Milan criteria with or without vascular invasion

Metastatic HCC
- With good liver function (Child-Pugh A or early B)
- With poor liver function

National Cancer Center Singapore Guidelines on Liver Cancer
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SGH – Surgery
<table>
<thead>
<tr>
<th>Clinical Presentation</th>
<th>Assessment</th>
<th>Treatment Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>EARLY STAGE HEPATOCELLULAR CANCER</td>
<td></td>
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</table>

### Clinical Presentation

**Early Stage HCC**

- Present for evaluation by Multi-disciplinary team

### Assessment

**Resectable**

- Lesions within the Milan Criteria with good functional status (Child-Pugh A, early B), adequate future liver remnant and good general health. Milan criteria [16,18-21] (level – 1a)
  - Solitary tumour ≤ 5cm OR ≤ 3 tumours, each < 3cm AND No macrovascular invasion and no distant metastases (pre-op imaging)*
  - RFA is an alternative in high risk resections [22-25] (level – 1a)

**Unresectable**

- Lesions within the Milan Criteria that cannot be resected because of
  - poor liver function [14, 26] (level –1b) or
  - inadequate future liver remnant [27,28] (level – 2b)
- Portal hypertension, varices, splenomegaly, sever ascites and platelet count

- Surgical resection*

- Imaging every 3-6 mo for 2 y, then every 6 mo [2,3] (level – 1a)
  - In the presence of microvascular invasion, imaging should be done every 3 months for 2 years and should include the chest [18] (level – 2b)
  - AFP, every 3-6 mo for 2 y, then every 6 mo
  - For relapse see Work Up Pathway, the relevant Stage and Treatment options

- Radio-frequency ablation for Lesions ≤ 3 lesions, each ≤ 3cm [23] (level – 1a)
- Transplantation [17] (level - 2b)
- External beam radiation can be considered for patient not suitable for transplant or RFA [29-31] (level – 1b)

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Surgery is potentially curative in Early Stage HCC
Systematic review of outcomes of liver resection for early hepatocellular carcinoma within the Milan criteria

K.-C. Lim¹, P. K.-H. Chow¹,²,³, J. C. Allen¹, F. J. Siddiqui¹,⁴, E. S.-Y. Chan¹,⁴ and S.-B. Tan¹,⁴

¹Centre for Quantitative Medicine, Duke–NUS Graduate Medical School, ²Department of General Surgery, Singapore General Hospital, ³Department of Surgical Oncology, National Cancer Centre, and ⁴Singapore Clinical Research Institute, Singapore

Correspondence to: Professor P. K.-H. Chow, c/o Department of General Surgery, Singapore General Hospital, Outram Road, Singapore 169608 (e-mail: pierce.chow@duke-nus.edu.sg)

2 RCT, 27 retrospective studies
Published between Jan 2000 – Dec 2010
4209 patients
with HCC within Milan Criteria
Med tumour size 2.5 – 4.0 cm

Med operative mortality 0.7% (0 – 5%)
Med 5-yr overall survival 67% (27 – 81)
Med 5-yr disease-free sur 37% (21 – 57)

Lim, Chow et al BJS 2012
Dynamic Assessment of Function

Indo-cyanine green retention test

Lau et al 1987: Relative risk of mortality for major hepatectomy increase 3X if ICG retention at 15 min > 14%

- Prospective study: 127 patients
Adequate Future Liver Remnant (FLR)

- **Normal liver** - FLR of at least 25% is deemed sufficient by most surgeons to prevent postoperative liver failure.
- **Cirrhotic Livers** - a larger FLR of up to 40% should be preserved\(^1,2\)
- **Inadequate FLR** is the most common factor precluding curative LR

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Courtesy Teo Jin Yao FRCS
The challenge of HCC

Surgery confers consistent long-term survival

But 80% are inoperable at time of diagnosis

- extensive disease
- inadequate liver function
- inadequate future liver remnant
**Clinical Presentation**

**Assessment**

**Treatment Options**

## EARLY STAGE HEPATOCELLULAR CANCER

<table>
<thead>
<tr>
<th>Early Stage HCC</th>
<th>Present for evaluation by Multidisciplinary team</th>
<th>Resectable</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>- Lesions within the Milan Criteria with good functional status (Child-Pugh A, early B), adequate future liver remnant and good general health. Milan criteria [16,18-21] (level – 1a)</td>
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<tr>
<td></td>
<td></td>
<td>- Solitary tumour ≤ 5cm OR ≤ 3 tumours, each &lt; 3cm AND No macrovascular invasion and no distant metastases (pre-op imaging)*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- RFA is an alternative in high risk resections [22-25] (level – 1a)</td>
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**Unresectable**

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- Portal hypertension, varices, splenomegaly, severe ascites and platelet count

**Surgical resection**

- Imaging every 3-6 mo for 2 y, then every 6 mo [2,3] (level – 1a)
- In the presence of microvascular invasion, imaging should be done every 3 months for 2 years and should include the chest [18] (level – 2b)
- AFP, every 3-6 mo for 2 y, then every 6 mo
- For relapse see Work Up Pathway, the relevant Stage and Treatment options

**Radio-frequency ablation for Lesions < 3 lesions, each < 3cm** [23] (level – 1a)

**Transplantation [17]** (level - 2b)

**External beam radiation can be considered for patient not suitable for transplant or RFA [29-31]** (level – 1b)

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http://www.nccs.com.sg/PatientCare/ComprehensiveLiverCancerClinic/Documents/CLCC guideline Final Ver to upload PDF 26092014.pdf
Radio-Frequency Ablation

- Radiofrequency ablation (RFA) is most efficacious for small volume HCC \( \leq 3 \text{ lesions each} \leq 3 \text{ cm} \)
- Mortality: 1.2%  Complications: 3 – 7%

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Tumor Size</th>
<th>Mortality Rate (%)</th>
<th>Major Morbidity Rate (%)</th>
<th>5-Yr Overall Survival (%)</th>
<th>5-Yr Disease-Free Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buscarini et al.(^{20}) 2001</td>
<td>88</td>
<td>(\leq 3.5 \text{ cm})</td>
<td>0</td>
<td>2.3</td>
<td>33</td>
<td>3</td>
</tr>
<tr>
<td>Lencioni et al.(^{21}) 2005</td>
<td>187</td>
<td>Mean, 2.8 cm</td>
<td>0</td>
<td>2.3</td>
<td>58</td>
<td>33.1</td>
</tr>
<tr>
<td>Raut et al.(^{22}) 2005</td>
<td>194</td>
<td>Median, 3.3 cm</td>
<td>1</td>
<td>12</td>
<td>55.4</td>
<td>33.1</td>
</tr>
<tr>
<td>Machi et al.(^{23}) 2005</td>
<td>65</td>
<td>Mean, 3.2 cm</td>
<td>1.2</td>
<td>4.8</td>
<td>39.9</td>
<td>27.9</td>
</tr>
<tr>
<td>Tateishi et al.(^{24}) 2005</td>
<td>319</td>
<td>Mean, 2.6 cm</td>
<td>0</td>
<td>4</td>
<td>54.3</td>
<td>—</td>
</tr>
<tr>
<td>Cabassa et al.(^{25}) 2006</td>
<td>59</td>
<td>Mean, 3.1 cm</td>
<td>0</td>
<td>1.7</td>
<td>43.1</td>
<td>—</td>
</tr>
<tr>
<td>Choi et al.(^{26}) 2007</td>
<td>570</td>
<td>Mean, 2.59 cm</td>
<td>0</td>
<td>1.9</td>
<td>58</td>
<td>21</td>
</tr>
</tbody>
</table>
# RFA vs Surgery for resectable HCC

## Meta-analysis of Randomized Controlled Trials

<table>
<thead>
<tr>
<th>Variables</th>
<th>No. studies furnishing data</th>
<th>Results</th>
<th>OR (95%CI)</th>
<th>P-value</th>
<th>I²</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>RFA</td>
<td>RES</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall survival</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-year</td>
<td>6 (22,25,30–33)</td>
<td>90.93%</td>
<td>94.95%</td>
<td>0.50 (0.29–0.86)</td>
<td>= 0.01</td>
</tr>
<tr>
<td>3-year</td>
<td>5 (22,25,30,31,33)</td>
<td>72.24%</td>
<td>81.09%</td>
<td>0.51 (0.28–0.94)</td>
<td>= 0.03</td>
</tr>
<tr>
<td>5-year</td>
<td>5 (22,30–33)</td>
<td>50.54%</td>
<td>60.41%</td>
<td>0.62 (0.45–0.84)</td>
<td>= 0.002</td>
</tr>
<tr>
<td>Recurrence-free survival</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-year</td>
<td>5 (22,25,30–32)</td>
<td>79.02%</td>
<td>83.30%</td>
<td>0.65 (0.44–0.97)</td>
<td>= 0.03</td>
</tr>
<tr>
<td>3-year</td>
<td>4 (22,25,30,31)</td>
<td>50.75%</td>
<td>58.95%</td>
<td>0.65 (0.47–0.89)</td>
<td>= 0.008</td>
</tr>
<tr>
<td>5-year</td>
<td>4 (22,30–32)</td>
<td>22.30%</td>
<td>33.58%</td>
<td>0.52 (0.35–0.77)</td>
<td>= 0.001</td>
</tr>
<tr>
<td>Overall survival in HCCs ≤ 3 cm</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-year</td>
<td>2 (22,31)</td>
<td>93.83%</td>
<td>99.04%</td>
<td>0.21 (0.04–1.15)</td>
<td>= 0.07</td>
</tr>
<tr>
<td>3-year</td>
<td>2 (22,31)</td>
<td>83.95%</td>
<td>93.27%</td>
<td>0.38 (0.16–0.89)</td>
<td>= 0.03</td>
</tr>
<tr>
<td>5-year</td>
<td>2 (22,31)</td>
<td>59.88%</td>
<td>69.23%</td>
<td>0.69 (0.41–1.16)</td>
<td>= 0.16</td>
</tr>
<tr>
<td>Local recurrence</td>
<td>3 (22,32,33)</td>
<td>17.04%</td>
<td>4.85%</td>
<td>4.08 (2.03–8.20)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Complication</td>
<td>4 (22,25,30–32)</td>
<td>6.58%</td>
<td>28.21%</td>
<td>0.29 (0.08–1.10)</td>
<td>= 0.07</td>
</tr>
</tbody>
</table>

CI, confidence interval; OR, odds ratio.

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SGH – Surgery

Li 2012
Earl Stage HCC

Present for evaluation by Multi-disciplinary team

Resectable
- Lesions within the Milan Criteria with good functional status (Child-Pugh A, early B), adequate future liver remnant and good general health. Milan criteria [16,18-21] (level – 1a)
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Surgical resection*

Radio-frequency ablation for Lesions ≤ 3 lesions, each ≤ 3cm [23] (level – 1a)

Imaging every 3-6 mo for 2 y, then every 6 mo [2,3] (level – 1a)
- In the presence of microvascular invasion, imaging should be done every 3 months for 2 years and should include the chest [18] (level – 2b)
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External beam radiation can be considered for patient not suitable for transplant or RFA [29-31] (level – 1b)

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Transplantation for Early stage HCC (within the Milan Criteria) inoperable, poor liver function

**Milan Criteria**

One lesion ≤ 5 cm  

or ≤ 3 lesions each ≤ 3 cm  

and no macro-vascular invasion

AASLD Management Guidelines 2010
5-year OS Transplantation for HCC

4482 patients with HCC
Intention to treat
5 year overall survival
Within Milan 61%
Outside Milan 32%

Actually transplanted
5 year overall survival
Within Milan 65%
Outside Milan 38%

Pelletier et al. 2009, Liver Transplantation

Figure 6. Overall intent-to-treat survival of patients listed for hepatocellular carcinoma according to the utilized criteria. There was a significant difference in survival among those that met the Milan criteria (black line) compared to those who exceeded the Milan criteria (black dotted line). The P value was < 0.0001.
# 5 year OS for Transplantation for HCC

**European Registry**  6874 HCC (1999 – 2009)

<table>
<thead>
<tr>
<th>Indication for LT</th>
<th>From 1998 to 2009</th>
<th></th>
<th>Last 10 years [1999-2009]</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Percentage (%)</td>
<td>Survival rate (%)</td>
<td>Percentage (%)</td>
<td>Survival rate (%)</td>
</tr>
<tr>
<td>No. of the patients</td>
<td>of the disease (%)</td>
<td>1</td>
<td>5</td>
<td>1</td>
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<tr>
<td>of the total (%)</td>
<td></td>
<td>10</td>
<td>15</td>
<td>20</td>
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<tr>
<td>Graft (%)</td>
<td>Patient (%)</td>
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<td>Primary liver tumors</td>
<td>14</td>
<td>72</td>
<td>76</td>
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<td>Hepatocellular carcinoma and cirrhosis</td>
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<td>Hepatocellular carcinoma and non-cirrhotic liver</td>
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<tr>
<td>Hepatic cholangiocellular carcinoma</td>
<td>332</td>
<td>3</td>
<td>0.4</td>
<td>2</td>
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EARLY STAGE HEPATOCELLULAR CANCER

**Clinical Presentation**: Present for evaluation by multi-disciplinary team

**Assessment**

**Resectable**
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**Treatment Options**

- **Surgical resection**
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(e-mail: pierce.chow@duke-nus.edu.sg)

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Med 5-yr disease-free sur 37% (21 – 57)

Lim, Chow et al BJS 2012
In early liver cancer with good liver function, resection is more cost effective in the US, Switzerland, Singapore.
Stages of Liver Cancer

Early Stage HCC
• Lesions within the Milan Criteria
• criteria:
  ➢ Solitary tumour \( \leq 5cm \) OR \( \leq 3 \) tumours, each \( < 3cm \) AND No invasion of blood vessels and no distant spread

Locally Advanced HCC
• Lesions confined to the liver that are outside of the Milan criteria with or without vascular invasion

Metastatic HCC
• With good liver function (Child-Pugh A or early B)
• With poor liver function

National Cancer Center Singapore Guidelines on Liver Cancer
http://www.nccs.com.sg/PatientCare/ComprehensiveLiverCancerClinic/Documents/CLCC guideline Final Ver to upload PDF 26092014.pdf

SGH – Surgery
**Clinical Presentation**

<table>
<thead>
<tr>
<th>Locally Advanced HCC</th>
<th>Treatment Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Present for evaluation by multi-disciplinary team</td>
<td>Consider Clinical Trial</td>
</tr>
<tr>
<td>Good liver function</td>
<td>Surgical resection for carefully selected cases after multidisciplinary board evaluation</td>
</tr>
<tr>
<td>Poor liver function</td>
<td>LOCOREGIONAL THERAPY</td>
</tr>
<tr>
<td>- Palliative treatment</td>
<td>No Vascular Invasion*</td>
</tr>
<tr>
<td>- Consider Clinical Trial</td>
<td>- Transarterial chemoembolisation (TACE) + DC-Beads [32,33] (level – 1b)</td>
</tr>
<tr>
<td>- Transplant within UCSF</td>
<td>- Selective Internal Radiation Therapy (SIRT) [34-36] (level – 2b)</td>
</tr>
<tr>
<td></td>
<td>- External beam RT (alone or as part of combined modality)</td>
</tr>
<tr>
<td></td>
<td>- Sorafenib [32-35] (level – 1b)</td>
</tr>
<tr>
<td>With Vascular Invasion</td>
<td></td>
</tr>
<tr>
<td>- Sorafenib [37-40] (level –1b)</td>
<td></td>
</tr>
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<tr>
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<td></td>
</tr>
<tr>
<td></td>
<td>Transplantation is a consideration for HCC within the USCF expanded criteria (single tumours &lt; 6.5cm or 2-3 tumours &lt; 4.5cm at the most, with a total tumour diameter &lt; 8cm) after assessment by a multi-disciplinary tumour board [43,44] (level – 2b)</td>
</tr>
</tbody>
</table>

*Sorafenib may also be considered when local regional therapy is not feasible or fails [40] (level - 2b)

---

**National Cancer Center Singapore Consensus Guidelines on Liver Cancer**

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Resection beyond the Milan Criteria

Shorter *survival*, Higher *recurrences*
Resection Exceeding the Milan criteria.
Lim KC, P Chow et al Ann Surg 2011

Resection with curative intent for HCC:
SGH\NCCS
Jan 2000 – Mar 2009
n = 454 (of 515 patients)

Median OS within Milan: 71.2 months
Median OS beyond Milan: 58.4 months

At risk, n
Milan- 213 149 68 31 16 6
Milan+ 241 198 112 60 33 11

p = 0.053
Impact of number of nodules on Overall Survival and Disease Free Survival: SGH/NCCS

Overall Survival: Total nodule ≤ 2 (N=651) versus total nodule >2 (N=51)

Median overall survival (month): 72.4
Total nodule ≤ 2: **79.6** (95%CI: 66.1 – 100.6)
Total nodule > 2: **21.7** (95%CI: 14.2 – 31.9)

log rank test: pv < 0.001

Disease Free Survival: Total nodule ≤ 2 (N=651) versus total nodule >2 (N=51)

Median disease-free survival (month): 22.7
Total nodule ≤ 2: **24.6** (95%CI: 20.5 – 30.1)
Total nodule > 2: **7.6** (95%CI: 4.8 – 10.7)

Log rank test:: pv 0.001

702 resections for HCC

Koh 2014 Unpublished data
Solitary Tumors – Impact of Size on Overall Survival and Disease Free Survival: SGH/NCCS

Overall Survival: Tumor size ≤7cm (N=427) versus tumor size >7cm (N=142)

Median overall survival (month):
- Tumor size≤7cm: 91.6 (95%CI: 71.2 – 112.6)
- Tumor size>7cm: 56.6 (95%CI: 39.0 – 101.9)

Log rank test: pv < 0.011

Disease Free Survival: Tumor size ≤7cm (N=427) versus tumor size >7cm (N=142)

Median disease-free survival (month):
- Tumor size≤7cm: 30.4 (95%CI: 23.8 – 36.9)
- Tumor size>7cm: 16.0 (95%CI: 10.1 – 25.0)

Log rank test: pv < 0.006

Koh 2014 Unpublished data
**LOCALLY ADVANCED HEPATOCELLULAR CARCINOMA**

<table>
<thead>
<tr>
<th>Clinical Presentation</th>
<th>Treatment Options</th>
</tr>
</thead>
<tbody>
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</tr>
<tr>
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<td></td>
</tr>
</tbody>
</table>

**LOCOREGIONAL THERAPY**

**No Vascular Invasion**
- Transarterial chemoembolisation (TACE) ± DC-Beads [32,33] (level – 1b)
- Selective Internal Radiation Therapy (SIRT) [34-36] (level – 2b)
- External beam RT (alone or as part of combined modality)
- Sorafenib [32-35] (level – 1b)

**With Vascular Invasion**
- Sorafenib [37-40] (level –1b)
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- External beam RT (alone or as part of combined modality) [41,42] (level – 2a)

- Transplantation is a consideration for HCC within the USCF expanded criteria (single tumours < 6.5cm or 2-3 tumours < 4.5cm at the most, with a total tumour diameter < 8cm) after assessment by a multi-disciplinary tumour board [43,44] (level – 2b)

*Sorafenib may also be considered when local regional therapy is not feasible or fails [40] (level - 2b)

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# OLT for HCC using UCSF Criteria

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Total Pts, n</th>
<th>Staging</th>
<th>Patients by Criteria, n</th>
<th>1 Yr Survival (%)</th>
<th>5 Yr Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Roayaie et al.¹⁵</td>
<td>2002</td>
<td>43</td>
<td>Imaging</td>
<td>—, Expanded: 32 *</td>
<td>—, 88</td>
<td>—, 55 *</td>
</tr>
</tbody>
</table>

*Based on tumor size 5–7 cm.

*Recurrence-free survival data.

*3-yr survival.

SGH – Surgery — single tumours < 6.5cm or 2-3 tumours < 4.5cm at the most, with a total tumour diameter < 8cm

Duffy, 2007
# Comparison of Criteria

<table>
<thead>
<tr>
<th>Study group/ Year</th>
<th>Total patients</th>
<th>Tumor Burden</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mazzaferro et al., 2009</td>
<td>1556</td>
<td>Beyond Milan Criteria up-to 7cm</td>
<td>5 year OS&lt;br&gt;*MI – 73.3%&lt;br&gt;*MO – 53.6%</td>
</tr>
<tr>
<td>Yao et al., 2007</td>
<td>168</td>
<td>UCSF Criteria&lt;br&gt;1 nodule ≤ 6.5cm, or 2-3 nodules ≤ 4.5cm and total tumor diameter ≤ 8cm</td>
<td>5 year OS&lt;br&gt;MI – 80%&lt;br&gt;MO – 82%</td>
</tr>
<tr>
<td>Zheng et al., 2008</td>
<td>141</td>
<td>Hangzhou criteria: total diameter &gt; 8 cm, grade 1-2, AFP &lt; 400</td>
<td>5 year OS&lt;br&gt;Within – 70.7%&lt;br&gt;Beyond – 18.9%</td>
</tr>
<tr>
<td>Tanka et al., 2003</td>
<td>56</td>
<td>Beyond Milan Criteria</td>
<td>TFS at 2 years&lt;br&gt;MI – 87%&lt;br&gt;MO – 76%</td>
</tr>
</tbody>
</table>

*MI – Inside Milan  *MO – Outside Milan
# Locally Advanced HCC

## Clinical Presentation
- Present for evaluation by multi-disciplinary team

## Treatment Options

### Locoregional Therapy

**No Vascular Invasion**
- Transarterial chemoembolisation (TACE) + DC-Beads [32,33] (level – 1b)
- Selective Internal Radiation Therapy (SIRT) [34-36] (level – 2b)
- External beam RT (alone or as part of combined modality)
- Sorafenib [32-35] (level – 1b)

**With Vascular Invasion**
- Sorafenib [37-40] (level – 1b)
- Selective Internal Radiation Therapy (SIRT) [34-36] (level – 2b)
- External beam RT (alone or as part of combined modality) [41,42] (level – 2a)

### Transplantation
- Transplantation is a consideration for HCC within the USCF expanded criteria (single tumours < 6.5cm or 2-3 tumours < 4.5cm at the most, with a total tumour diameter < 8cm) after assessment by a multi-disciplinary tumour board [43,44] (level – 2b)

*Sorafenib may also be considered when local regional therapy is not feasible or fails [40] (level - 2b)

---

**National Cancer Center Singapore Consensus Guidelines on Liver Cancer**

[Link](http://www.nccs.com.sg/PatientCare/ComprehensiveLiverCancerClinic/Documents/CLCC guideline Final Ver to upload PDF 26092014.pdf)
Main Loco-regional Therapies

• Trans-arterial chemo-embolisation (TACE):
  • widely used - disease control approx 40%
  • used mainly in HCC, NETs (includes DC Beads)

• Selective Internal Radiation Therapy (SIRT):
  • higher disease control (approx 80%)
  • SIR-Sphere®, Thera-Sphere®
Trans-arterial chemo-embolization

- **Injecting** chemotherapy (*doxorubicin, cisplatin, mitomycin*) via femoral -> hepatic artery (with embolization)
- Requires good liver function (Child’s A)
- complete regression (*CR*) uncommon (2%).
- Most commonly used
Overall Survival (OS) in TACE

Table 4. RCTs Assessing Arterial Embolization/Chemoembolization Versus Conservative Management/Suboptimal Therapies as a Primary Treatment for Nonsurgical HCC

<table>
<thead>
<tr>
<th>Author, Journal, Year (Patients)</th>
<th>Treatment Arm</th>
<th>N</th>
<th>1 yr</th>
<th>2 yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lin et al., Gastroenterology, 1988 (n = 63)</td>
<td>Embolization</td>
<td>21</td>
<td>42</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td>Embolization + IV 5-fluorouracil</td>
<td>21</td>
<td>19</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>IV 5-fluorouracil</td>
<td>21</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>Pelletier et al., J Hepatol, 1990 (n = 42)</td>
<td>Chemoembolization (Doxorubicin)</td>
<td>21</td>
<td>24</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>Conservative management</td>
<td>21</td>
<td>33</td>
<td>NA</td>
</tr>
<tr>
<td>Madden et al., Gut, 1993 (n = 50)</td>
<td>Chemoembolization (Epirubicin)</td>
<td>25</td>
<td>16</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>Conservative management</td>
<td>25</td>
<td>16</td>
<td>NA</td>
</tr>
<tr>
<td>GETCH, N Engl J Med, 1995 (n = 96)</td>
<td>Chemoembolization (Cisplatin)</td>
<td>50</td>
<td>62</td>
<td>38</td>
</tr>
<tr>
<td></td>
<td>Conservative management</td>
<td>46</td>
<td>43</td>
<td>26</td>
</tr>
<tr>
<td>Bruix et al., HEPATOLOGY, 1998 (n = 80)</td>
<td>Embolization + coils</td>
<td>40</td>
<td>70</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>Conservative management</td>
<td>40</td>
<td>72</td>
<td>50</td>
</tr>
<tr>
<td>Pelletier et al., J Hepatol, 1998 (n = 73)</td>
<td>Chemoembolization (Cisplatin)</td>
<td>37</td>
<td>51</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>Tamoxifen</td>
<td>36</td>
<td>55</td>
<td>25</td>
</tr>
<tr>
<td>Llovet et al., Lancet 2002 (n = 112)</td>
<td>Embolization</td>
<td>37</td>
<td>75</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>Chemoembolization (Adriamycin)</td>
<td>40</td>
<td>82</td>
<td>63</td>
</tr>
<tr>
<td></td>
<td>Conservative management</td>
<td>35</td>
<td>63</td>
<td>27</td>
</tr>
</tbody>
</table>

Lo CM  Hepatology 2002
Cisplatin + lipiodol + gelatin  40  57  31
BSC  40  32  11

Post-embolization syndrome can be very severe

Bruix 2003
2-year OS
24 – 63%
Main Loco-regional Therapies

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  • widely used - disease control approx 40%
  • used mainly in \textit{HCC, NETs} (includes DC Beads)

• Selective Internal Radiation Therapy (SIRT):
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  • SIR-Sphere®, Thera-Sphere®
Trans-arterial Route

Yttrium-90 on microspheres:

- 20 – 40 μm diameter
- High-energy beta rays 0.9367 MeV
- 64.2 hrs (2.67 days) half-life
- Penetration:
  - average penetration 2.5mm
  - maximum range 11.0mm

Ideal for Brachy-therapy
Post-therapy Bremsstrahlung

Catheter-directed CT Hepatic Angiogram

Yttrium-90 time-of-flight PET/CT has superior spatial resolution than bremsstrahlung SPECT/CT
• **Mainly Hepatitis C/alcohol**

• **Median Survival:** **12.8 months** *(95% CI: 10.9-15.7)*
  - BCLC B: **16.9 months**
  - BCLC C: **10.0 months**

• Failed or progressed on prior therapy **41.5%**
  - Trans-arterial therapy **27.4%**
  - Surgery/transplantation **18.2%**
  - Percutaneous ablative therapy **9.2%**
• Mainly **Hepatitis B**
• Median Survival: **14.4 months** (95% CI, 11.0 – 2.2)
  • BCLC B: **23.8 months**
  • BCLC C: **11.8 months**
• Failed or progressed on prior therapy **55.4%**
  • Trans-arterial therapy **17.5%**
  • Surgery/transplantation **14.6%**
  • Percutaneous ablative therapy **12.6%**
  • Chemotherapy **10.7%**
# Downstaging with SIRT or TACE in HCC

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Number</th>
<th>Overall survival months</th>
<th>TTP months</th>
<th>Response&lt;sup&gt;a&lt;/sup&gt;, %</th>
<th>Downstaged/transplanted %</th>
<th>Days in hospital&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lewandowski et al. [41] (2009)</td>
<td>TARE (glass) TACE</td>
<td>43</td>
<td>35.7</td>
<td>33.3</td>
<td>61</td>
<td>86</td>
<td>58&lt;sup&gt;c&lt;/sup&gt; 31</td>
</tr>
<tr>
<td>Kooby et al. [42] (2010)</td>
<td>TARE (resin) TACE</td>
<td>27</td>
<td>6</td>
<td>NR</td>
<td>11</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Carr et al. [43] (2010)</td>
<td>TARE (glass) TACE</td>
<td>99</td>
<td>11.5&lt;sup&gt;d&lt;/sup&gt;</td>
<td>NR</td>
<td>41</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Salem et al. [44] (2011)</td>
<td>TARE (glass) TACE</td>
<td>123</td>
<td>20.5</td>
<td>13.3</td>
<td>49</td>
<td>72</td>
<td>25&lt;sup&gt;c&lt;/sup&gt; 36</td>
</tr>
</tbody>
</table>

Most studies used a chemotherapy combination of mitomycin/doxorubicin/cisplatin with lidipol for TACE. In Carr et al. [43], cisplatin was used alone with lipiodol.

TTP = Time to tumor progression; NR = not reported; WHO = World Health Organization tumor response criteria.

<sup>a</sup> Response: patients with complete or partial response.  
<sup>b</sup> Mean days in hospital per treatment.  
<sup>c</sup> Significant difference, p < 0.05.
Stages of Liver Cancer

Early Stage HCC
• Lesions within the Milan Criteria
• criteria:
  ➢ Solitary tumour ≤ 5cm OR ≤ 3 tumours, each < 3cm AND No invasion of blood vessels and no distant spread

Locally Advanced HCC
• Lesions confined to the liver that are outside of the Milan criteria with or without vascular invasion

Metastatic HCC
• With good liver function (Child-Pugh A or early B)
• With poor liver function

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SGH – Surgery
HCC is highly resistant to conventional systemic chemotherapy

- In spite of many phase III clinical trials, previously no survival advantage with any systemic therapy for advanced HCC
- 1st positive phase III trial: July 2007, Sorafenib – an oral molecular targeted therapy

Novak, Chow, Findlay 2004
Sorafenib: proposed mechanism

Tumor cell proliferation

- EGF
- PDGF
- VEGF
- Proliferation
- Survival

- Ras
- Raf
- MEK
- ERK
- Nucleus

- Apoptosis

Tumor angiogenesis

- PDGF-β
- VEGF
- PDGFR-β
- Ras
- Raf
- MEK
- ERK
- Nucleus

- Angiogenesis

Paracrine stimulation

Sorafenib: proposed mechanism

Wilhelm SM et al. Cancer Res 2004
Results of the phase III sorafenib Trial
(Asia-Pacific patients) 2009
Child-Pugh A ECOG 0 - 1

Overall Survival

Time to Progression

Improvement in survival of 2.3 months
**Clinical Presentation**

**Metastatic HCC**

- Present for evaluation by Multi-disciplinary team at TBM

**Treatment Options**

**Patients with good liver function (Child-Pugh A or B)**

- Systemic therapy
  - **Sorafenib** (Child-Pugh Class A or B) [38,46] (level – 1b)
- Consideration for clinical trial
- Palliative RT as appropriate

**Patients with poor liver function**

- Best supportive care
- Consideration for clinical trial
- Palliative RT as appropriate) [30] (level – 1a)

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National Cancer Center Singapore Consensus Guidelines on Liver Cancer

[http://www.nccs.com.sg/PatientCare/ComprehensiveLiverCancerClinic/Documents/CLCC guideline Final Ver to upload PDF 26092014.pdf](http://www.nccs.com.sg/PatientCare/ComprehensiveLiverCancerClinic/Documents/CLCC guideline Final Ver to upload PDF 26092014.pdf)
Rapid Evolution in the Management of HCC

• The last decade has seen better approaches and more efficacious therapies for HCC e.g.
• Much greater number of options
• The rapid evolution has lead to significant improvement in clinical outcomes
• New clinical trial data will lead to additional changes in management over the next few years
Thank You!