Hepatocellular Carcinoma: Transplantation, Resection or Ablation?

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Transplant Service Line
University of Kentucky
Disclosure

• Nothing to disclose
Objective

• Discuss basic principles in Hepatocellular Carcinoma treatment
Hepatocellular Carcinoma

- Represents the fourth most common cause of cancer-related deaths worldwide
- Risk Factors: HCV, HBV
- Incidence: from 1970 to 1990, 1.4 to 3.0 per 100000, in 2010 is 6 per 100000
- HCC in HCV infection will continue to rise and will peak in 2019
- Men has 3-fold increased risk

El-Serag H, Hepatology, Feb 2015
Hepatocellular Carcinoma Treatment

- Size
- Number of Lesions
- Function (Child’s)
- Vascular Invasion
- Extrahepatic Disease
Hepatocellular Carcinoma Treatment

- Liver Transplantation
- Resection
- Ablation (MWA, RFA)
- TACE
- Radio-embolization
- Chemotherapy and Radiotherapy
- Molecular Targeted Therapies
Resection

- Only 20%
- Liver Function (Child’s A)
- No portal hypertension (splenomegaly or low platelet count)
- No extrahepatic disease

Bruix J et al., Hepatology 1997
## Resection

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>1 yr</th>
<th>3 yr</th>
<th>5 yr</th>
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<tbody>
<tr>
<td>Sasaki et al, 1987 (109)</td>
<td>101</td>
<td>30</td>
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<td>Belghiti et al, 1991 (110)</td>
<td>47</td>
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<td>Capussotti et al, 1994 (14)</td>
<td>33</td>
<td>32</td>
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<td>88</td>
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<td>Yamamoto et al, 1996 (68)</td>
<td>229</td>
<td>20</td>
<td>70</td>
<td>83</td>
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<td>Fuster et al, 1996 (102)</td>
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<td>22</td>
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<table>
<thead>
<tr>
<th>Study</th>
<th>Number of Patients</th>
<th>1-Year Survival (%)</th>
<th>3-Year Survival (%)</th>
<th>5-Year Survival (%)</th>
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<td>Franco et al, 1990 (31)</td>
<td>43</td>
<td>66</td>
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<td>Ringe et al, 1991 (12)</td>
<td>18</td>
<td>—</td>
<td>—</td>
<td>42</td>
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<tr>
<td>Bismuth et al, 1993 (20)</td>
<td>46</td>
<td>—</td>
<td>39</td>
<td>—</td>
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<tr>
<td>Kawasaki et al, 1995 (33)</td>
<td>93</td>
<td>73</td>
<td>54</td>
<td>40</td>
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<tr>
<td>Lee et al, 1996 (34)</td>
<td>48</td>
<td>—</td>
<td>68</td>
<td>50</td>
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<tr>
<td>Nakajima et al, 1996 (35)</td>
<td>50</td>
<td>90</td>
<td>75</td>
<td>53</td>
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<tr>
<td>Beaujon, 1998*</td>
<td>122</td>
<td>82</td>
<td>55</td>
<td>33</td>
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</tbody>
</table>

* Unpublished data.
Resection

- Solitary lesions
- No vascular invasion
- Size <5cm
- Margin 1cm
- 5-year survival 78%
Incurable by Resection

- Invasion of a major portal or hepatic vein
- Direct invasion of organs other than the gallbladder
- Nodal or distant metastases
Liver Transplantation

- One Tumor <5cm
- Less than 3 lesions <3cm
- No extrahepatic disease
- 5 year survival rate 60-70%

Liver Transplantation: Allocation

- Initially listed with their functional MELD
- MELD 28 at 6 months
- Capped at MELD 34
Liver Transplantation: Bridging therapy

- AASLD guidelines
- UNOS T2
- To decrease dropout
- Waiting more than 6 months
- TACE, Ablation, Y90
- AASLD does not recommend one specific form of therapy over another
- Benefits remain unclear
Liver Transplantation: Downstaging

- **TACE, Y90, Ablation**
- **Systematic review showed 48% success rate**
- **Downstage within Milan**
- **AASLD guidelines:**
  - Patients beyond the Milan criteria after downstaging into the Milan criteria
- **AFP levels**

Parikh ND et al, Liver Transpl. 2015
RISING INCIDENCE OF NONALCOHOLIC STEATOHEPATITIS AMONG PATIENTS TRANSPLANTED FOR HEPATOCELLULAR CARCINOMA IN THE UNITED STATES

1Roberto Gedaly, MD; 1Davenport DL, PhD; 1Michael F. Daily, MD; 1M Shah, MD; 1Jonathan C. Hundley, MD; 1Lucy Dagher MD; 2Paul Angulo, MD  ASSLD
Alpha-fetoprotein and tumour size are associated with microvascular invasion in explanted livers of patients undergoing transplantation with hepatocellular carcinoma

Patrick P. McHugh¹, Jeffrey Gilbert¹, Santiago Vera², Alvaro Koch¹, Dinesh Ranjan¹ & Roberto Gedaly¹

¹Transplant Center, University of Kentucky College of Medicine, Lexington, KY, and ²Transplantation Institute, Methodist Hospital, University of Tennessee Medical School, Memphis, TN, USA

• 101 patients
• Predictors of survival and tumor recurrence
• Predictors of microvascular invasion

HBP, 2010
Liver Transplant

- Median Size 2.6 ±1.5 cm (range 0.7-10 cm)
- Perioperative mortality 4%
- Recurrence 11%

Gedaly R et al HBP, 2010
Liver Transplant

- Predictors of survival
  - Microvascular Invasion OR 4.70
  - Lymph nodes OR 6.05
- Predictors of recurrence
  - Microvascular Invasion
- Predictors of Microvascular Invasion
  - Size (OR 4.1)
  - AFP>100 (OR 5.0)

Gedaly R et al HBP, 2010
No Microvascular Invasion
92%, 78% and 72%

Gedaly R et al HBP, 2010
Conclusion

• Excellent results can be obtained in selected patients with survival rates above 70% at 5 years

• AFP and tumor size are strongly associated with microvascular invasion

• Microvascular invasion is independently associated with poor outcomes
Cancer stem cell marker expression alone and in combination with microvascular invasion predicts poor prognosis in patients undergoing transplantation for hepatocellular carcinoma

Valery Vilchez, M.D., Lilia Turcios, Ph.D., Yekaterina Zaytseva, Ph.D., Rachel Stewart, D.O., Eun Y. Lee, M.D., Erin Maynard, M.D., Malay B. Shah, M.D., Michael F. Daily, M.D., Ching-Wei D. Tzeng, M.D., Daniel Davenport, Ph.D., Ana Lia Castellanos, M.D., Steven Krohmer, M.D., Peter J. Hosein, M.D., Bernard Mark Evers, M.D., Roberto Gedaly, M.D.,

\(^{a}\)Department of Surgery, University of Kentucky, Lexington, KY, USA; \(^{b}\)Department of Surgery, Cleveland Clinic Foundation, Cleveland, OH, USA; \(^{c}\)Markey Cancer Center - University of Kentucky, Lexington, KY, USA; \(^{d}\)Departments of Pathology, \(^{e}\)Radiology, and \(^{f}\)Internal Medicine, University of Kentucky, Lexington, KY, USA
AIMS

- To determine the correlation of expression of CD133 and CD44 with AFP levels and tumor differentiation

- To study the association of LCSC marker expression (CD133 and CD44) in conjunction with MVI with patients outcomes
## TUMORS CHARACTERISTICS

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. (%) or mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of tumors</td>
<td></td>
</tr>
<tr>
<td>Solitary lesion</td>
<td>41 (43)</td>
</tr>
<tr>
<td>Multiple lesions</td>
<td>54 (57)</td>
</tr>
<tr>
<td>Size (cm)</td>
<td>2.38 ± 1.36</td>
</tr>
<tr>
<td>Microvascular invasion (MVI)</td>
<td>22 (23)</td>
</tr>
<tr>
<td>Incidental</td>
<td>30 (32)</td>
</tr>
<tr>
<td>Capsular invasion</td>
<td>8 (8)</td>
</tr>
<tr>
<td>Moderate-poorly differentiated</td>
<td>66 (70)</td>
</tr>
<tr>
<td>Lymph node invasion</td>
<td>2 (2)</td>
</tr>
<tr>
<td>TNM classification</td>
<td></td>
</tr>
<tr>
<td>T1N0M0</td>
<td>34 (35.8)</td>
</tr>
<tr>
<td>T2N0M0</td>
<td>54 (56.8)</td>
</tr>
<tr>
<td>T3AN0M0</td>
<td>5 (5.3)</td>
</tr>
<tr>
<td>T3AN1M0</td>
<td>2 (2.1)</td>
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</tbody>
</table>

SD = standard deviation.
CD133+ tumors were independently associated with levels of AFP > 100 mg/dl

<table>
<thead>
<tr>
<th>Independent Variables</th>
<th>Odds Ratio</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGE</td>
<td>1.08</td>
<td>0.150</td>
</tr>
<tr>
<td>GENDER</td>
<td>0.68</td>
<td>0.571</td>
</tr>
<tr>
<td>CD133+</td>
<td>10.34</td>
<td>0.036</td>
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</table>
### PREDICTORS OF TUMOR DIFFERENTIATION

<table>
<thead>
<tr>
<th>Independent Variables</th>
<th>Odds Ratio</th>
<th>p-value</th>
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<tbody>
<tr>
<td>AGE</td>
<td>0.90</td>
<td>0.146</td>
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<tr>
<td>GENDER</td>
<td>0.28</td>
<td>0.24</td>
</tr>
<tr>
<td>CD133+/CD44+</td>
<td>0.12</td>
<td>0.026</td>
</tr>
<tr>
<td>AFP &gt; 100mg/dl</td>
<td>0.14</td>
<td>0.016</td>
</tr>
</tbody>
</table>

CD133+/CD44+ tumors and AFP levels were significantly associated with moderate to poorly differentiated HCC.
CD44+ expression and MVI in the explanted tumors was an independent predictor of recurrence and survival (recurrence p < 0.003, OR = 8.05 survival p < 0.001, HR 3.7)
CD133+ expression and MVI in the explanted tumors was an independent predictor of recurrence and survival (recurrence p<0.001, OR= 9.5 survival p<0.004, HR 3.2)
CONCLUSIONS

• CD133$^+$ tumors were significantly associated with elevated levels of AFP (10 fold)

• CD133$^+$/CD44$^+$ tumors and AFP levels were independently associated with moderate to poorly differentiated HCC

• Patients with MVI and positive expression of CD44 or CD133 had 5-year survival rates lower than those with MVI alone
ORIGINAL ARTICLE

Long-term outcome of patients undergoing liver transplantation for mixed hepatocellular carcinoma and cholangiocarcinoma: an analysis of the UNOS database

Valery Vilchez\textsuperscript{1}, Malay B. Shah\textsuperscript{1}, Michael F. Daily\textsuperscript{1}, Luis Pena\textsuperscript{2}, Ching-Wei D. Tzeng\textsuperscript{1}, Daniel Davenport\textsuperscript{1}, Peter J. Hosein\textsuperscript{3}, Roberto Gedaly\textsuperscript{1} & Erin Maynard\textsuperscript{1}

\textsuperscript{1}Department of Surgery, University of Kentucky, College of Medicine, \textsuperscript{2}Department of Gastroenterology, and \textsuperscript{3}Department of Internal Medicine, University of Kentucky, Lexington, KY, 40536, USA
LT FOR PRIMARY LIVER MALIGNANCY

UNOS Database

4,049 patients have been transplanted for primary liver malignancy
94 HCC-CC - 3,515 HCC - 440 CC
<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>1 year</th>
<th>3 year</th>
<th>5 year</th>
<th>10 year</th>
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<tbody>
<tr>
<td>HCC-CC (n=94)</td>
<td>82</td>
<td>47</td>
<td>40</td>
<td>40</td>
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<tr>
<td>HCC (n=3515)</td>
<td>86</td>
<td>72</td>
<td>62</td>
<td>44</td>
</tr>
<tr>
<td>CC (n=440)</td>
<td>79</td>
<td>58</td>
<td>47</td>
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</tbody>
</table>
Ablation Therapy

Radiofrequency

• Less than 3-4cms
• Not surgical candidates
• Bridge to OLT
• 4-Year Survival Rates of 45%
Review Article

The Role of Bridging Therapy in Hepatocellular Carcinoma

Roberto Galuppo, Angie McCall, and Roberto Gedaly

Department of Surgery, College of Medicine, University of Kentucky, Lexington, KY 40536-0293, USA

Correspondence should be addressed to Roberto Gedaly; rgeda2@uky.edu

Received 16 March 2013; Revised 10 October 2013; Accepted 10 October 2013
Molecular Targeted Therapies

- Advanced disease
- Improved Survival 7.8 to 10.7 months, placebo vs. Sorafenib p<0.05
- Tumor progression

In-Vitro
PI103 + Sorafenib
Combination significantly inhibit EGF stimulated HCC proliferation by Blocking Ras/Raf/MAPK and PI3K/AKT/mTOR pathways
The Role of PI3K/mTOR Inhibition in Combination with Sorafenib in Hepatocellular Carcinoma Treatment

ROBERTO GEDALY\(^1\), PAUL ANGULO\(^2\), CHANGGUO CHEN\(^1\), KATE TOWNSEND CREASY\(^3,4\), BRETT T. SPEAR\(^3,4\), JONATHAN HUNDLEY\(^1\), MICHAEL F. DAILY\(^1\), MALAY SHAH\(^1\) and B. MARK EVERS\(^1,4\)

Departments of \(^1\)Surgery, \(^2\)Internal Medicine, \(^3\)Immunology and \(^4\)Markey Cancer Center, University of Kentucky, College of Medicine, Lexington, KY, U.S.A.

- In-Vivo
- PI103 + Sorafenib
- Combination significantly inhibit tumor progression
- Increased apoptosis

### Drug Induced Apoptosis in Tumors
(Assayed by Cleaved PARP)

![Graph showing drug-induced apoptosis](image)

Figure 2. Growth curves of tumor xenografts. Mice were treated with sorafenib and PI-103 as single agents or in combination. *Control significantly different from mono-drug or drug-combination treatments (p<0.05); **drug-combination treatment significantly different from mono-drug treatments (p<0.032).
PKI-587 and sorafenib alone and in combination on inhibition of liver cancer stem cell proliferation

Roberto Gedaly, MD, a, * Roberto Galuppo, MD, a Yolanda Musgrave, MD, b Paul Angulo, MD, c Jonathan Hundley, MD, a Malay Shah, MD, a Michael F. Daily, MD, a Changguo Chen, PhD, a Donald A. Cohen, PhD, d Brett T. Spear, PhD, d and B. Mark Evers, MD a,e

Fig. 2 – PKI-587 and sorafenib synergistically inhibited LCSC proliferation detected by MTT assay.
Signaling pathways in HCC
Targeting the Wnt/β-Catenin Signaling Pathway in Liver Cancer Stem Cells and Hepatocellular Carcinoma Cell Lines with FH535

Roberto Gedaly¹, Roberto Galuppo¹, Michael F. Daily¹, Malay Shah¹, Erin Maynard¹, Changguo Chen¹, Xiping Zhang², Karyn A. Esser², Donald A. Cohen³, B. Mark Evers⁴, Jieryun Jiang⁴, Brett T. Spear⁴

¹ Department of Surgery, University of Kentucky, Lexington, Kentucky, United States of America, ² Department of Physiology, University of Kentucky, Lexington, Kentucky, United States of America, ³ Department of Microbiology, Immunology & Molecular Genetics, University of Kentucky, Lexington, Kentucky, United States of America, ⁴ Markey Cancer Center, University of Kentucky, Lexington, Kentucky, United States of America

Effect of FH535 on LCSC Cell Cycle

Cyclin-D1
Survivin
β-Actin
New Wnt/B-catenin inhibitors
Cancer Immunotherapy

HEP3B  HUH7  PLC

PDL1

PDL2
Conclusions

• Surgery should be considered in patients without significant PH, small lesions and good functional reserve

• Transplantation is probably the best option in patients within Milan criteria and those that can be down-staged
Conclusions

- Ablation should be considered in patients with less than 3-4 lesion less than 3-4cms each if surgery is contraindicated
- Bridging Therapy indicated in T2 HCC
- Downstaging is useful in selected cases