HCC : Liver Resection and Transplantation

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None conflict of interest to declare
# Hepatic resection or liver transplantation?

<table>
<thead>
<tr>
<th>RESECTION</th>
<th>TRANSPLANTATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Questionable mortality in non tertiary referring center</td>
<td>Acceptable operative mortality in most transplant centers</td>
</tr>
<tr>
<td>No treatment of cirrhosis</td>
<td>Cure for cirrhosis</td>
</tr>
<tr>
<td>High recurrence rate</td>
<td>Low recurrence rate</td>
</tr>
<tr>
<td>Limited indications</td>
<td>Limited indications</td>
</tr>
<tr>
<td>Low cost</td>
<td>High cost</td>
</tr>
<tr>
<td>Always available</td>
<td>Organ depending availability</td>
</tr>
<tr>
<td>Needs well trained surgeons</td>
<td>Needs transplant surgeons</td>
</tr>
</tbody>
</table>
Resection or liver transplantation? 1999-2016

**Bologna cases: 1588 LTs**

- Re-transplantation: 11%
- Acute hepatic failure: 3.6%
- HCC on cirrhosis: 29%
- Post-necrotic cirrhosis: 39%
- Alcoholic cirrhosis: 8%
- Primary biliary cirrhosis: 4%
- Sclerosing cholangitis: 3%
- Other: 2.4%
- Primary biliary cirrhosis: 4%
- Benign tumors: 11%
- Hydatid cysts: 2.4%
- Colangiocarcinoma: 5%
- Metastases: 35%
- Others: 6.3%
- HCC: 10%
- Klatskin tumor: 3.3%
- Trauma: 1%
- HCC on cirrhosis: 25%

**Bologna cases: 2693 LRs**
LT and LR: T 1 (50 LT and 27 LR) 1999-2012

Survival analysis graph showing liver transplantation and liver resection with 0,0 - 1,0 survival rates over 0,0 - 60,0 time periods.
LT and LR: T 2 (216 LT and 257 LR) 1999-2012
LT and LR: T 3 (56 LT and 98 LR) 1999-2012

T3 down-staged to T2 before LT
Survival at 1-year
>80% BCLC 0-A-B

Survival at 5-year
BCLC 0  80%
BCLC A  70%
BCLC B  50%
Controversies in surgical indications

1. Very early stage (0)
   Single <2 cm
   Carcinoma in situ

2. Portal pressure and/or bilirubin
   Increased
   Normal

3. Early stage (A)
   Single or 3 nodules ≤3 cm
   PST 0

4. Intermediate stage (B)
   Multinodular
   PST 0

5. Advanced stage (C)
   Portal invasion
   N1, M1, PST 1–2

6. Terminal stage (D)

7. Stage 0
   PST 0, Child–Pugh A

8. Stage A–C
   PST 0–2, Child–Pugh A–B

9. Stage D
   PST >2, Child–Pugh C

Resection
Liver transplantation (DDLT/LDLT)
RF/PEI
TACE
Sorafenib
Best supportive care

Curative treatment (30–40%)
Median OS >60 months; 5-year survival: 40–70%

Target: 20%
OS: 20 months
(SD 14–45)

Target: 40%
OS: 11 months
(SD 6–14)

Target: 10%
OS: <3 months
Expanding the room for hepatic resection
1- very early HCCs

RFA can be more cost-effective than HR. This finding is currently included in the EASL-EORTC guidelines.

After propensity score matching analysis, SR was associated with better OS compared with RFA (P = 0.034).

Expanding the room for hepatic resection
1- very early HCCs

Alpha1fetoprotein > 200 ng/ml was introduced as an inclusion criterion to improve diagnosis accuracy.

Microscopic vascular invasion involves 20% of tumors of 2 cm and this proportion linearly increase with AFP levels.

Expanding the room for hepatic resection
2- increased bilirubin/portal pressure

- Resection is the first-line treatment option for patients with solitary tumors and very well-preserved liver function, defined as normal bilirubin with either hepatic venous pressure gradient ≤10 mmHg or platelet count ≥100,000
  (evidence 2A; recommendation 1B)
  Anatomical resections are recommended
  (evidence 3A; recommendation 2C)

- Additional indications for patients with multifocal tumors meeting Milan criteria (≤3 nodules ≤3 cm) or with mild portal hypertension not suitable for liver transplantation require prospective comparisons with loco-regional treatments
  (evidence 3A; recommendation 2C)

- Peri-operative mortality of liver resection in cirrhotic patients is expected to be 2-3%

- Neo-adjuvant or adjuvant therapies have not proven to improve outcome of patients treated with resection (or local ablation)
  (evidence 1D; recommendation 2C)

- Tumor recurrence represents the major complication of resection and the pattern of recurrence influences subsequent therapy allocation and outcome. In case of recurrence, the patient will be re-assessed by BCLC staging, and re-treated accordingly
Expanding the room for hepatic resection
2- increased bilirubin

Bilirubin levels did not affect survival after surgery:

Liver resection for BCLC C?

Right portal vein infiltration and Neoplastic thrombosis
Liver resection for HCC with Portal Hypertension?

RIGTH HEPATECTOMY with LEFT PORTAL VEIN reconstruction, Vena cava and left portal vein tumor thrombectomy; preservation of round ligament

Post-operative outcome: absence of liver failure and no blood transfusions; discharge IX post-op. with-out complications
Expanding the room for hepatic resection 
2- portal pressure

70 patients submitted to R0 resection for HCC with preoperative HVPG measurement.

0% 90 days post-operative mortality.

Fig. 1. Postoperative course of MELD score at different time points of patients with and without HVPG \( \geq 10 \text{ mmHg} \). POD = postoperative day. For both patients with HVPG value <10 mmHg and \( \geq 10 \text{ mmHg} \) the median delta-MELD between 90-days and preoperative values was zero (IQR: 0–1). The mean change of MELD was 0.2 in patients with HVPG <10 mmHg and of 0.8 in patients with HVPG \( \geq 10 \text{ mmHg} \).

Expanding the room for hepatic resection

2- portal pressure

50% of patient with “high” HVPG experienced an uneventful post-operative outcome.

Expanding the room for hepatic resection 3- (Large?) and multinodular HCCs

In the present case, the median survival was about 20 months, with a 5-year survival rate of only 7% (Child-Pugh class A). Comparing this figure with available literature it became evident that surgery would produce more medical benefit, with a median survival of about 60 months.

Expanding the room for hepatic resection

4- Presence of portal vein tumor invasion

- Sorafenib is the standard systemic therapy for HCC. It is indicated for patients with well-preserved liver function (Child-Pugh A class) and with advanced tumors (BCLC C) or those tumors progressing upon loco-regional therapies (evidence 1iA; recommendation 1A)

- There are no clinical or molecular biomarkers available to identify the best responders to sorafenib (evidence 1A; recommendation 2A)

- Systemic chemotherapy, tamoxifen, immunotherapy, anti-androgen, and herbal drugs are not recommended for the clinical management of HCC patients (evidence 1-2A; recommendation 1A/B)

- There is no available second-line treatment for patients with intolerance or failure to sorafenib. Best supportive care or the inclusion of patients in clinical trials is recommended in this setting (recommendation 2B)

- In specific circumstances, radiotherapy can be used to alleviate pain in patients with bone metastasis (evidence 3A; recommendation 2C)

- Patients at BCLC D stage should receive palliative support including management of pain, nutrition and psychological support. In general, they should not be considered for participating in clinical trials (recommendation 2B)
Expanding the room for hepatic resection

4- Presence of portal vein tumor invasion

Expanding the room for hepatic resection

4- Presence of portal vein tumor invasion

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**TABLE 2.** Pattern of Presentation According to the BCLC Classification

<table>
<thead>
<tr>
<th>BCLC Class</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BCLC 0-A [n = 931]</strong></td>
<td></td>
</tr>
<tr>
<td>Single ≤2 cm</td>
<td>204 (22)</td>
</tr>
<tr>
<td>Single ≤5 cm</td>
<td>604 (65)</td>
</tr>
<tr>
<td>Up to 3 tumors, none &gt;3 cm</td>
<td>123 (13)</td>
</tr>
<tr>
<td><strong>BCLC B [n = 666]</strong></td>
<td></td>
</tr>
<tr>
<td>Single &gt;5 cm</td>
<td>456 (68.5)</td>
</tr>
<tr>
<td>Multiple</td>
<td>210 (31.5)</td>
</tr>
<tr>
<td><strong>BCLC C [n = 222]</strong></td>
<td></td>
</tr>
<tr>
<td>PV invasion</td>
<td>60 (27)</td>
</tr>
<tr>
<td>First-order PV</td>
<td>20 (9)</td>
</tr>
<tr>
<td>Second-order PV</td>
<td>16 (7)</td>
</tr>
<tr>
<td>Third-order PV</td>
<td>24 (11)</td>
</tr>
<tr>
<td>HV invasion</td>
<td>77 (35)</td>
</tr>
<tr>
<td>IVC invasion</td>
<td>15 (7)</td>
</tr>
<tr>
<td>PV + HV invasion</td>
<td>63 (28)</td>
</tr>
<tr>
<td>PV + IVC invasion</td>
<td>—</td>
</tr>
<tr>
<td>HV + IVC invasion</td>
<td>7 (3)</td>
</tr>
</tbody>
</table>

*The number of patients for whom the data were available.
HV indicates hepatic vein; IVC, inferior vena cava; PV, portal vein.

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Median survival of PVT patients is about 36 months!

Expanding the room for hepatic resection
Radio-embolization as conversion therapy

When evaluating patients for resection, two aspects can qualify the possible unresectability of the tumour. [1] the close proximity of the tumour to vital hepatic structures that can make any type of intervention impossible. [2] the presence of an inadequate future liver remnant.

Table 1. Summary of literature reporting response rates of HCC/CCC after radio-embolization

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Patients n*</th>
<th>SIRT modality</th>
<th>Tumor response criteria</th>
<th>Tumor Response rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mazzaferrro (2013)</td>
<td>52</td>
<td>Glass</td>
<td>EASL</td>
<td>CR: 9.6%; OR: 40.4%</td>
</tr>
<tr>
<td>Salem (2011)</td>
<td>123</td>
<td>Glass</td>
<td>WHO/RECIST</td>
<td>OR: 49%</td>
</tr>
<tr>
<td>Hilgard (2010)</td>
<td>108</td>
<td>Glass</td>
<td>WHO/RECIST</td>
<td>OR: 41% (CR 6%; PR 35%)</td>
</tr>
<tr>
<td>Salem (2010)</td>
<td>291</td>
<td>Glass</td>
<td>EASL</td>
<td>OR: 57% (CR 23%; PR 34%)</td>
</tr>
<tr>
<td>Kooby (2010)</td>
<td>27</td>
<td>Resin</td>
<td>WHO/RECIST</td>
<td>PR: 11%</td>
</tr>
<tr>
<td>Carr (2010)</td>
<td>99</td>
<td>Glass</td>
<td>WHO/RECIST</td>
<td>OR: 41% (CR 3%; PR 38%)</td>
</tr>
<tr>
<td>Lewandowski (2009)</td>
<td>43</td>
<td>Glass</td>
<td>WHO/RECIST</td>
<td>PR: 61% (CR 0%)</td>
</tr>
<tr>
<td>Kulik (2008)</td>
<td>108</td>
<td>Glass</td>
<td>EASL</td>
<td>OR: 86% (CR 47%; PR 39%)</td>
</tr>
<tr>
<td>Songro (2006)</td>
<td>24</td>
<td>Resin</td>
<td>WHO/RECIST</td>
<td>PR: 42%</td>
</tr>
<tr>
<td>Salem (2005)</td>
<td>43</td>
<td>Glass</td>
<td>WHO/RECIST</td>
<td>PR: 47%</td>
</tr>
<tr>
<td>Carr (2004)</td>
<td>65</td>
<td>Glass</td>
<td>WHO/RECIST</td>
<td>PR: 38.4%</td>
</tr>
</tbody>
</table>

Complete response (CR) rate is reported to be about 10% with an objective response (OR) rate of about 40%.

Cappelli et al. Liver Cancer. 2016 in press
Expanding the room for hepatic resection
Radio-embolization as conversion therapy

When evaluating patients for resection, two aspects can qualify the possible unresectability of the tumour. [1] the close proximity of the tumour to vital hepatic structures that can make any type of intervention impossible. [2] the presence of an inadequate future liver remnant.

Increase in the future liver remnant (FLR) volume at 3 months after RE ranging between 21 and 32%: the longer the follow-up, the greater the amount of hypertrophy that can be obtained.

**Key message:** RE in unresectable HCC can provide a shrinkage of the tumour allowing resectability (?).

The hypertrophy of the contra-lateral lobe can help in achieving safer major hepatectomies.

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Cappelli et al. Liver Cancer. 2016 in press
Expanding the room for hepatic resection
Radio-embolization as conversion therapy

M.P. male 72 y. Chronic hepatitis C. HCC of the caudate lobe in between the right and the left hepatic veins with neoplastic infiltration of the left portal vein. CTP A, no comorbidities, HVPG = 13mmHg but biased from tumor compression on the hepatic veins.
Expanding the room for hepatic resection
Radio-embolization as conversion therapy

RADIOEMBOLIZATION: selective catheterism of the afferent hepatic artery and infusion of Sirtex® dose, evaluating the distribution of Ittrium90 during the procedure. No post-procedural sequelae. 3 month control: OBJECTIVE RESPONSE.

MAIN SURGICAL PROBLEM: even if reduced in size and most necrotic, the tumor is surrounded by fibrotic peri-tumoral tissue that can still not allow for disengagement of right hepatic vein and of vena cava

⇒ PLANNED INTERVENTION: LEFT HEPATECTOMY WITH VENO-VENOUS BY-PASS AND VASCULAR RECONSTRUCTIONS
Expanding the room for hepatic resection
Radio-embolization as conversion therapy
Expanding the room for hepatic resection
Radio-embolization as conversion therapy

- Atrial cannula
- Iliac vein cannula
- De-flow through caval opening
- Splanchnic flow
- Cold perfusion of the right hemi-liver
Expanding the room for hepatic resection
Radio-embolization as conversion therapy

ICE in the right diaphragmatic lodge
Perfusion of right hemi-liver with 2L of Celsion
Expanding the room for hepatic resection
Radio-embolization as conversion therapy

Clamp on the portal vein
Clamp on the RHA
Transection with Sonosurg
Expanding the room for hepatic resection
Radio-embolization as conversion therapy

RHV (detached from the tumor)
Caval ostium
Goretex reconstruction
Expanding the room for hepatic resection
Radio-embolization as conversion therapy
Expanding the room for Liver Transplantation

Transplant is the only chance for cure

Liver Transplantation represents the only chance for “cure” of HCC. Statistical cure is achieved when a transplant patient return to have the same age- and sex-matched mortality of the general population.

Can Liver Transplantation Provide the Statistical Cure?

Alessandro Cucchetti, Alessandro Vitale, Matteo Cescon, Martina Gambato, Lorenzo Maroni, Matteo Ravaiol, Giorgio Ercolani, Patrizia Burra, Umberto Cillo, and Antonio D. Pinna

1Department of Medical and Surgical Sciences, Sant’Orsola-Malpighi Hospital, University of Bologna, Bologna, Italy; and 2Hepatobiliary Surgery and Liver Transplant Unit, Department of General Surgery and Organ Transplantation, and 3Multivisceral Transplant Unit, Department of Surgery, Oncology, and Gastroenterology, University of Padua, Padua, Italy

Overall, the probability of being cured from hepatic disease with transplantation is about 63% and the time to achieve 90% of certainty is about 10 years.
Expanding the room for Liver Transplantation

Transplant is the only chance for cure

Bologna - Padua experience between January 1999 and December 2012.

<table>
<thead>
<tr>
<th>TABLE 2. Estimation of Cure Fractions and Survival for Uncured Transplant Patients Stratified by Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (n)</td>
</tr>
<tr>
<td>---------------</td>
</tr>
<tr>
<td>All patients</td>
</tr>
<tr>
<td>Bologna patients</td>
</tr>
<tr>
<td>Padua patients</td>
</tr>
<tr>
<td>Recipient age &lt; 55 years</td>
</tr>
<tr>
<td>Recipient age ≥ 55 years</td>
</tr>
<tr>
<td>Male patients</td>
</tr>
<tr>
<td>Female patients</td>
</tr>
<tr>
<td>HCV-positive</td>
</tr>
<tr>
<td>HCV-negative</td>
</tr>
<tr>
<td>Alcoholic disease</td>
</tr>
<tr>
<td>Cholestatic disease</td>
</tr>
<tr>
<td>Other etiologies</td>
</tr>
<tr>
<td>Presence of HCC</td>
</tr>
<tr>
<td>Absence of HCC</td>
</tr>
<tr>
<td>MELD score &lt; 17</td>
</tr>
<tr>
<td>MELD score ≥ 17</td>
</tr>
<tr>
<td>Donor age &lt; 58 years</td>
</tr>
<tr>
<td>Donor age ≥ 58 years</td>
</tr>
</tbody>
</table>

NOTE: Continuous variables have been categorized on the basis of their median values (see Table 1).
*The values within parentheses are 95% confidence intervals.
Expanding the room for Liver Transplantation
Expanding the donor pool

UNOS database
540 HCVneg donors
Vs
540 HCVpos donors (RNA not provided)
P>0.500

HCV-positive donors can go similar to HCV-negative donors

Expanding the room for Liver Transplantation Priority and response to bridge therapies

Exploring biology: T2 tumors with complete response to bridge therapies have the same risk of drop-out than T1

Adopted as priority criteria in Emilia Romagna since 2012.

Expanding the room for Liver Transplantation
Priority and response to bridge therapies

Meeting Report

A Multistep, Consensus-Based Approach to Organ Allocation in Liver Transplantation: Toward a “Blended Principle Model”

U. Cillo1, P. Burra2*, V. Mazzaferrro3, L. Belli4, A. D. Pinna5, M. Spada6, A. Nanni Costa7 and P. Toniutto9 on behalf of the I-BELT (Italian Board of Experts in the Field of Liver Transplantation)

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2Multivisceral Transplant Unit, Gastroenterology, Department of Surgery, Oncology and Gastroenterology, Padova University Hospital, Padova, Italy
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*Corresponding author: Patrizia Burra, burra@unipd.it

Since Italian liver allocation policy was last revised in 2009, several advances and consequent changes associations and organ-sharing organizations, transplant coordinators, and ethicists voted on and validated the proposed statements. After carefully reviewing the statements, a critical proposal for revising Italy’s current liver allocation policy was prepared jointly by transplant surgeons and hepatologists.

Abbreviations: AIF, Italian Association for the Study of the Liver; HCC, hepatocellular carcinoma; LT, liver transplantation; MELD, model for end-stage liver disease; NTC, National Transplantation Center; OPTN, Organ Procurement and Transplantation Network; SITO, Italian Society for Organ Transplantation; TN, nontransplantable; TT, transplantable; UNOS, United Network for Organ Sharing

Received 06 October 2014, revised 01 May 2015 and accepted for publication 09 May 2015

Introduction

Allocation systems relying mainly on the principle of urgency, like those prioritizing patients with higher MELD scores, have several inherent weaknesses because MELD score measures severity of disease, but often fails to predict outcome after liver transplantation (LT) (1). MELD scores also cannot gauge the severity of several diseases currently considered “MELD exceptions,” or of hepatocellular carcinoma (HCC) in patients with compensated
Expanding the room for Liver Transplantation Priority and response to bridge therapies

**FIG. 1.** Staging and allocation for HCC within the spectrum of LT eligibility. Classes of progression and allocation priority within the TT stages identified for HCC in well-compensated cirrhosis. LT eligibility and priority are not determined completely up front, but they both come into focus after the best available therapy has been applied. Details on application rules are given in Table 1.
Expanding the room for Liver Transplantation
Downstaging protocol

B

Actuarial intention-to-treat survival

Bologna criteria with down-stage (B.C.D.S.)
48 pts

→ 5 pts unable to complete the protocol (all died)

→ 43 pts listed for LT

2 pts died on list from liver failure

→ 32 pts had LT

→ 9 pts died after LT

→ 23 alive after LT

→ 27 pts alive (56%)

Conventional criteria (C.C.)
129 pts

→ 129 pts listed for LT

→ 15 pts excluded for tumor progression (2 pts still alive)

→ 14 pt still alive on waiting list

→ 88 pts had LT

→ 23 pts died after LT

→ 65 alive after LT

→ 81 pts alive (62.8%)

Figure 2: (A) Intention-to-treat survival since patient evaluation for liver transplantation according to the study group: conventional criteria (CC) versus extended criteria with the down-staging protocol (BCDS). (B) Actuarial intention-to-treat outcome since patient evaluation at every treatment steps according to the study group: conventional criteria (CC) versus extended criteria with the down-staging protocol (BCDS).

Downstaging protocol
Results updated to 120 patients

$P=N.S.$

Survival after LT years

Update Am J Transplant 2008; 8: 2547–57
Down-stage results: survival Bologna up-date

Survival after LT years

$P < 0.05$

Up-date Am J Transplant 2008; 8: 2547–57
Expanding the room for Liver Transplantation
Super-downstaging protocol

Patient with HCC and type I-II MaVI without extra-hepatic spread and medical conditions able to contraindicate liver transplantation

- Radio-embolization with Y-90 microspheres
- 3-month evaluation with CT scan + CEUS
- Complete radiological response & serum AFP<100 ng/mL

  - No
  - Yes

  - Re-treatment with Y-90 / TACE / RFA
  - 6-month (from the date of RE) evaluation with CT scan +/- CEUS

  - Complete radiological response & serum AFP<100 ng/mL

    - No
    - Yes

    - Listing for liver transplantation

      - Cadaveric donor
      - Living donor
Expanding the room for Liver Transplantation
Superdownstaging

H.S. maschio di 53 anni, epatite cronica HBV. HCC del 5° - 8° segmento con trombosi tipo II. MELD: 9, Child – Pugh class A, non significative comorbidità. Fibroscan 34 kPa. HVPG 22mmHg. Intervento richiesto per l’asportazione mesoepatectomia ritenuta troppo a rischio per insufficienza epatica post-operatoria.

Si opta per radioembolizzazione e studio OLT
Expanding the room for Liver Transplantation
Superdownstaging

RADIOEMBOLIZZAZIONE → controllo 6 mesi: RISPOSTA COMPLETA

Downstaging protocol
Results updated to 120 patients

Survival after LT years

Up-date Am J Transplant 2008; 8: 2547–57
Hepatic resection and liver transplantation for HCC

2000-2010: why hepatic resection instead of primary liver transplantation?

Bologna: January 1998 and December 2010: 951 First Liver Transplantation

The hazard rate of mortality in respect to the general population become negligible after 5-6 years from LT = statistical cure!

Cucchetti et al. Liver Transpl. 2014;20:210-7
Hepatic resection and liver transplantation for HCC

2000-2010: why hepatic resection instead of primary liver transplantation?

Bologna: January 1998 and December 2010: 951 First Liver Transplantation

The hazard rate of HCV+ practically never become negligible after 5-6 years from LT

= little chances for cure for these patients

Cucchetti et al. Liver Transpl. 2014;20:210-7
Hepatic resection and liver transplantation for HCC

2000-2010: why hepatic resection instead of primary liver transplantation?

Bologna: January 1998 and December 2010: 951 First LT – causes of death (HCV+)

Cumulative incidence

Months

Infection
HCV recurrence
Miscellaneous
CV-Neurological
MOF
Tumor (de-novo or recurrence)
Hepatic resection and liver transplantation for HCC

2000-2010: why hepatic resection instead of primary liver transplantation?

Make a choice:

Primary transplantation with the risk of untreated HCV recurrence and patient death...

Or try to procrastinate as much as possible liver transplantation?

Salvage transplantation
Hepatic resection and liver transplantation
Bologna’s update to 368 patients

<table>
<thead>
<tr>
<th></th>
<th>Primary LT (N=331)</th>
<th>Salvage SLT (N=37)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender M/F</td>
<td>274 (83%)/57 (17%)</td>
<td>32 (86%)/ 5 (13%)</td>
<td>N.S.</td>
</tr>
<tr>
<td>Recipient age (yrs)</td>
<td>54.4 ± 7.44</td>
<td>53.4 ± 11.2</td>
<td>N.S.</td>
</tr>
<tr>
<td>MELD</td>
<td>17.2 ± 7.6</td>
<td>15.2 ± 8.19</td>
<td>N.S.</td>
</tr>
<tr>
<td>Number of nodules</td>
<td>1.90 ± 1.5 (0-9)</td>
<td>3.78 ± 2.53 (1-8)</td>
<td>0.001</td>
</tr>
<tr>
<td>Diameter (cm)</td>
<td>1.45 ± 13.9 (0-6.5)</td>
<td>1.00 ± 10.8 (0-5)</td>
<td>N.S.</td>
</tr>
<tr>
<td>AFP (ng/mL)</td>
<td>27.4 ± 80.96</td>
<td>6.62 ± 25.29</td>
<td>N.S.</td>
</tr>
<tr>
<td>G3-4</td>
<td>190 (57%)</td>
<td>18 (50%)</td>
<td>N.S.</td>
</tr>
<tr>
<td>MVI</td>
<td>131 (40%)</td>
<td>17 (46%)</td>
<td>N.S.</td>
</tr>
<tr>
<td>I.O. Blood transfusion</td>
<td>2699 ± 2811 cc</td>
<td>2646 ± 3298 cc</td>
<td>N.S.</td>
</tr>
<tr>
<td>Hospital mortality</td>
<td>3.3%</td>
<td>0</td>
<td>N.S.</td>
</tr>
<tr>
<td>Re-LT</td>
<td>5.4%</td>
<td>5.1%</td>
<td>N.S.</td>
</tr>
<tr>
<td>Biliary complications</td>
<td>17.2</td>
<td>16.2%</td>
<td>N.S.</td>
</tr>
<tr>
<td>Vascular complications</td>
<td>6%</td>
<td>0</td>
<td>N.S.</td>
</tr>
<tr>
<td>Infections</td>
<td>19.3%</td>
<td>5.4%</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>HCC recurrence</td>
<td>10%</td>
<td>13%</td>
<td>N.S.</td>
</tr>
</tbody>
</table>
Hepatic resection and liver transplantation
Bologna’s update to 368 patients

Overall survival

Disease-free survival

P=NS

Primary LT
Salvage LT

78.5%
71.7%

73.8%
70.8%

Up-date data of Am J Transpl. 2008; 8:1177-1185
Hepatic resection and liver transplantation
Bologna’s update to 368 patients

Intention to treat analysis

590 pts listed for LT (1996-2011):

- 368 (64%) liver transplantations
- 84 (14.2%) dead on waiting list
- 73 (12.4%) dropout related to HCC
- 23 (3.9%) on the waiting list
- 21 (3.6%) temporarily in stand-by due to good clinical conditions

Up-date data of Am J Transpl. 2008; 8:1177-1185
Expanding the room for Liver Transplantation

The changing scenario

<table>
<thead>
<tr>
<th>Study</th>
<th>Percent Sustained Virologic Response (%)</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burton et al. 2014</td>
<td>63</td>
<td>81</td>
</tr>
<tr>
<td>Forns et al. 2014</td>
<td>72</td>
<td>74</td>
</tr>
<tr>
<td>Forns et al. 2014</td>
<td>62</td>
<td>85</td>
</tr>
<tr>
<td>Charlton et al. 2014</td>
<td>70</td>
<td>40</td>
</tr>
<tr>
<td>Brown et al. 2014</td>
<td>90</td>
<td>68</td>
</tr>
<tr>
<td>Reddy et al. 2014</td>
<td>92</td>
<td>112</td>
</tr>
<tr>
<td>Kuo et al. 2014</td>
<td>97</td>
<td>34</td>
</tr>
</tbody>
</table>

Burton et al. 2014: PEG/RBV + BOC or TVR (48 weeks)
Forns et al. 2014: PEG/RBV + TVR (48 weeks)
Forns et al. 2014: SOF/RBV ± PEG (24-48 weeks)
Charlton et al. 2014: SOF/RBV (24 weeks)
Brown et al. 2014: SOF/SIM ± RBV (12 weeks)
Reddy et al. 2014: SOF/LED/RBV (12 weeks)
Kuo et al. 2014: ABT-450/ir/ombitasvir + dasabuvir + RBV (24 weeks)
OVERALL survival after LT for HCC is the summary of two main competing events

Death for causes different from HCC recurrence

And, in particular, in HCV patients, the hepatitis recurrence...

By avoiding HCV recurrence by DAA we can increase this specific survival

Death because of HCC recurrence

Allowing to accept higher rates of tumor recurrence?
Expanding the room for Liver Transplantation
The changing scenario

- Re-formulate the indications to liver transplantation in the light of new antiviral (HCV) agents (DAAs)
- Re-formulate the indications to liver transplantation in relationship with biological behaviour of the tumor
- Role on the decision-making for Hepatic resection + Salvage transplantation versus primary transplantation
- Expanding safety the donor pool by using grafts from anti-HCV+ donors
The possibility to effectively treat the HCV after liver transplantation can shift the decision-making choice from resection+salvage to primary liver transplantation.

The increase of post-LT SVR achievement will lead to increased 5-year survival.
Expanding the room for Liver Transplantation
Expanding the donor pool

HCV-recurrence-free survival: donor HCV-RNA negative go the same as anti-HCV negative. Can the possibility to “negativise” the donor produce the same outcome?

Expanding the room for Liver Transplantation
The changing scenario

- Re-formulate the indications to liver transplantation in the light of new antiviral (HCV) agents (DAAs)
- Re-formulate the indications to liver transplantation in relationship with biological behaviour of the tumor

  - Response to therapy as priority criteria for liver transplantation
  - Response to therapy in HCC outside Milan criteria but within «downstaging criteria»
  - Response to therapy in HCC with tumoral macroscopic vascular invasion («superdownstaging»)
### Hepatic resection and liver transplantation: the changing scenario

1359 LT for HCC performed between 2000-2013 (Bo-Mi1-Mi2-Fudan)

<table>
<thead>
<tr>
<th></th>
<th>Training set (Western n: 1018)</th>
<th>Validation set (Eastern n: 341)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean; SD; years)</td>
<td>55.9 (7.0)</td>
<td>51.9 (9.2)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Cause of cirrhosis*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>579 (56.9%)</td>
<td>9 (2.6%)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>327 (32.1%)</td>
<td>328 (96.2%)</td>
<td></td>
</tr>
<tr>
<td>Number of vital tumors</td>
<td></td>
<td></td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>None (complete response after bridge)</td>
<td>355 (37.3%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Single nodule</td>
<td>325 (34.1%)</td>
<td>211 (61.9%)</td>
<td></td>
</tr>
<tr>
<td>2-3 nodules</td>
<td>230 (24.1%)</td>
<td>86 (25.2%)</td>
<td></td>
</tr>
<tr>
<td>More than 3 nodules</td>
<td>43 (4.5%)</td>
<td>44 (12.9%)</td>
<td></td>
</tr>
<tr>
<td>Largest vital tumor (cm)</td>
<td></td>
<td></td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>2.5 (1.4)</td>
<td>3.8 (2.6)</td>
<td></td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>2.0 (1.5 – 3.0)</td>
<td>3.0 (2.0 – 4.7)</td>
<td></td>
</tr>
<tr>
<td>Last AFP (median; IQR; ng/mL)</td>
<td>8.3 (4 – 22)</td>
<td>32.9 (6.6 – 232.9)</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

OUTCOMES!
**Hepatic resection and liver transplantation: the changing scenario**

1359 LT for HCC performed between 2000-2013 (Bo-Mi1-Mi2-Fudan)

<table>
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<tr>
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<th>Training set (Western n: 1018)</th>
<th>Validation set (Eastern n: 341)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall Survival</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3-yr</td>
<td>83.3%</td>
<td>78.1%</td>
<td>.423</td>
</tr>
<tr>
<td>5-yr</td>
<td>78.0%</td>
<td>74.9%</td>
<td></td>
</tr>
<tr>
<td><strong>Recurrence-free Survival</strong></td>
<td></td>
<td></td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>3-yr</td>
<td>89.6%</td>
<td>81.0%</td>
<td></td>
</tr>
<tr>
<td>5-yr</td>
<td>87.4%</td>
<td>77.9%</td>
<td></td>
</tr>
<tr>
<td><strong>HCC-specific Survival</strong></td>
<td></td>
<td></td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>3-yr</td>
<td>93.4%</td>
<td>84.4%</td>
<td></td>
</tr>
<tr>
<td>5-yr</td>
<td>91.6%</td>
<td>82.0%</td>
<td></td>
</tr>
</tbody>
</table>

Despite larger tumors, lower recurrence-free survival and HCC-specific survival, the overall survival was similar between Western and Eastern patients!
Hepatic resection and liver transplantation: the changing scenario

NEW METROTICKET based on radiological features

5-year incidence of HCC-related death

Num+Diam=6 & AFP = 100ng/mL

Number + Diameter Vital Tumors

- 70%-80%
- 60%-70%
- 50%-60%
- 40%-50%
- 30%-40%
- 20%-30%
- 10%-20%
- 0%-10%
Hepatic resection and liver transplantation: the changing scenario

NEW METROTICKET based on radiological features

5-year HCC-related death is between 20-30%

If HCV (untreated or unsuccessful to DAA)
+18.1% mortality
Overall 5-y mortality between 38-48%
Overall 5-y survival between 52-62%

If HCV negative (or treated successfully with DAA)
+8.6% mortality
Overall 5-y mortality between 29-39%
Overall 5-y survival between 61-71%

Num+Diam=6 & AFP = 100ng/mL

Legend:
- 70%-80%
- 60%-70%
- 50%-60%
- 40%-50%
- 30%-40%
- 20%-30%
- 10%-20%
- 0%-10%
Resection or liver transplantation?

Conclusions

Hepatic resection remains the first option for HCC in cirrhosis Child A / MELD < 10-12 with or without portal hypertension but PLT > 50000 and no high risk oesophageal varices

Liver transplantation may be a combined treatment with hepatic resection and the results should be analyzed with the intention-to-treat principle
Resection or liver transplantation?

Conclusions

*Patient selection and Functional/Tumor staging are still a matter of debate for surgical resection and for LT*

*Surgical strategies should consider many variables:*

- tumor histology
- patient age, comorbidities, liver function, portal hypertension
- donor pool, expected mean time in waiting list for LT
- Type of liver disease.