Management and Treatment of HCC is Optimized in a Multidisciplinary Liver Tumor Board

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Overview

- Treatment landscape of HCC is rapidly evolving with expansion of treatment choices

- In the USA, the HCC incidence rate has more than doubled over the past two decades and is anticipated to continue to increase. How can we improve overall care to HCC patients?

- Role of multidisciplinary tumor board in highlighting controversial areas in diagnosis and treatment of HCC
PR Galle et al. Modified BCLC staging system: 2018
Working as a multidisciplinary team improves the outcome and provides outcome benefit for all HCC stages

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Period</th>
<th>No. of patients</th>
<th>Outcomes</th>
</tr>
</thead>
</table>
| Yopp et al\textsuperscript{32} | USA     | Pre: 2006–2010          | Pre: 250        | • Shorter time to treatment
• Reduced stage-adjusted mortality |
|                  |         | Post: 2010–2011         | Post: 105       |                                                                          |
| Serper et al\textsuperscript{33} | USA     | 2008–2014               | Total: 3,988    | • Increased treatment receipt
• Reduced mortality |
|                  |         |                         | Multidisciplinary tumor board (MDT): 1,366    |                                                                          |
|                  |         |                         | Multidisciplinary care: 2,155       |                                                                          |
| Chang et al\textsuperscript{31}  | USA     | Pre: 2000–2003          | Pre: 62         | • Increased treatment receipt
• Reduced mortality |
|                  |         | Post: 2003–2006         | Post: 121       |                                                                          |
| Sinn et al\textsuperscript{34}   | Korea   | Pre: 2000–2005          | Pre: 5,881      | • Reduced mortality |
| Agarwal\textsuperscript{40}      | USA     | Pre: 2002–2011          | Pre: 349        | • Increased treatment receipt
• Reduced mortality |
| Gashin et al\textsuperscript{36} | USA     | 2009–2010               | 137             | • Increased treatment receipt
• Reduced mortality
• Not following MDT decision was a negative prognostic factor |
| Duininck\textsuperscript{41}     | USA     | Pre: 2009–2012          | Pre: 70         | • Increased treatment receipt
• Reduced mortality |
|                  |         | Post: 2013–2016         | Post: 134       |                                                                          |
| Zhang et al\textsuperscript{30}  | USA     | 2009–2012               | 343             | • Alterations to imaging and pathology
• Interpretation for diagnosis
• Changes in management plan |
| Charriere et al\textsuperscript{35} | France  | 2006–2013               | 387             | • Not following MDT decision was a negative prognostic factor |

Kia Byrd, MD, MPH\textsuperscript{1}  Saleh Alqahtani, MD\textsuperscript{2,3}  Adam C. Yopp, MD, MS\textsuperscript{4}  Amit G. Singal, MD, MS\textsuperscript{1}
 Poor care HCC quality in the post-MELD exception era

- SEER registry data demonstrate very low treatment rates, even for early-stage HCC in US patients, with 43% of patients within Milan criteria not undergoing surgery, ablation, or transplantation.

• N = 3988
• 128 VA centers in the US (69% academic, 31% community-based)

Most patients had ECOG performance status of ≤2.

Nearly 36% of patients presented with early-stage HCC (BCLC stages 0 or A).

• 18% had macrovascular invasion, and 7.2% had metastatic disease.
Only 25% of early stage (BCLC 0-A) patients initially received guideline-recommended therapy with curative intent.

Even among a subset of the fittest patients with potentially curable disease (BCLC stages 0-A, CTP A cirrhosis, and ECOG performance status 0–2) 13% did not receive any active treatment.
Multivariate analysis of factors influencing All-Cause mortality in HCC patients

- Specialist (hepatology, medical oncology, surgery) seen within 30 days of HCC diagnosis and MDT review: associated with better overall survival.

<table>
<thead>
<tr>
<th>Provider factors</th>
<th>HR for mortality</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specialist seen within 30 days of diagnosisd</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatology</td>
<td>0.7</td>
<td>0.63–0.78</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Medical oncology</td>
<td>0.82</td>
<td>0.74–0.91</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Surgery</td>
<td>0.79</td>
<td>0.71–0.89</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Gastroenterology</td>
<td>1.02</td>
<td>0.93–1.13</td>
<td>0.673</td>
</tr>
<tr>
<td>Palliative care</td>
<td>2.1</td>
<td>1.87–2.36</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>No specialist</td>
<td>0.89</td>
<td>0.65–1.21</td>
<td>0.447</td>
</tr>
<tr>
<td>Evaluation by ≥1 specialist</td>
<td>1.09</td>
<td>0.96–1.23</td>
<td>0.187</td>
</tr>
<tr>
<td>Multidisciplinary tumor board</td>
<td>0.83</td>
<td>0.77–0.90</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

hepatology care, while not associated with higher odds of receiving active therapy, was associated with a 30% mortality reduction.
Multidisciplinary liver tumor board (MDT) for HCC patients

MDTs have become standard of care in many centers for cancer patients including for HCC.
Potential challenges about MDT meetings

- Decisions made in MDT meetings can be associated with an unconscious bias within the group, can affect individual decisions and the outcome of MDT discussion.

- Previous adverse event caused by a treatment modality affects individual medical decision making.

- The role of MDT leader is important in maintaining the discussion within the framework of available evidence and resources and facilitating an effective communication and discussion.
Models for multidisciplinary care

- Presentation of the cases at MDT occurs either retrospectively after patients had already been seen or prospectively.

- Multidisciplinary clinics divided into 2 models:
  a) patients seen same day in co-located clinic rooms concurrently by providers from multiple specialties. [Improves pt satisfaction and time to treatment; challenges: may result in lost clinical revenue by seeing less pts by each provider, difficulty with clinic logistics]
  b) patients seen sequentially by specialists on different days
liver cancer-specific virtual tumor boards (VTBs)

- Telehealth-based VTB have strong potential to reduce diagnostic delays and to speed development of treatment plans.

- Telehealth technologies can reduce geographic barriers to access to the VTBs.
HOW does MDT improve outcome in HCC patients?

Clinical decision making in areas of uncertainty
In contrast to most other cancers, diagnosis of HCC is typically made by characteristic radiographic features on dynamic multiphasic CT or MRI using LIRADS criteria (Liver Imaging Reporting and Data System), v2018.

Beyond diagnosis, radiologists play a critical role in determining intrahepatic tumor burden as well as the presence of any vascular involvement or distant metastases. This can be particularly challenging in patients with possible bland versus tumor thrombus or patients with mildly enlarged lymph nodes.
MDT improves diagnosis accuracy

- In a single-center study among 269 patients with malignant lesions, of whom 95 had HCC, presentation at a multidisciplinary tumor board changed imaging and histological interpretation in 18.4 and 10.9% of patients, respectively.

- Diagnosis and management plans were altered in 8.4 and 41.7% of patients, respectively.

LI-RADS and AASLD now have identical criteria for definite HCC.
LI-RADS and OPTN now have almost identical criteria for HCC, with one exception (below).

**Exception:** 10-19 mm + APHE + nonperipheral “washout” = LR-5, but does not meet OPTN Class 5 criteria
CT or MRI diagnostic LIRADS features: LR-5

<table>
<thead>
<tr>
<th>Major Feature</th>
<th>Definition</th>
<th>Examples</th>
</tr>
</thead>
</table>
| Nonrim arterial phase hyperenhancement (APHE)     | Nonrim-like enhancement in arterial phase unequivocally greater in whole or in part than liver. Enhancing part must be higher in attenuation or intensity than liver in arterial phase. | CT: Arterial phase  
MRI-ECA: Arterial phase  
MRI-Gadoxetate: Arterial phase |
|                                                   | **Comment:** Nonrim APHE is required for LR-5 categorization.             |                                                                          |
| Non peripheral washout appearance ("washout")    | Nonperipheral visually assessed temporal reduction in enhancement in whole or in part relative to composite liver tissue from earlier to later phase resulting in hypoenhancement in the extracellular phase:  
• portal venous or delayed phase with ECA or gadobenate  
• portal venous phase with gadoxetate                  | CT: Portal or delayed phase  
MRI-ECA: Portal or delayed phase  
MRI-Gadoxetate: Portal phase only |
| Enhancing capsule appearance ("capsule")         | Smooth, uniform, sharp border around most or all of an observation, unequivocally thicker or more conspicuous than fibrotic tissue around background nodules, and visible as as enhancing rim in portal venous phase, delayed phase, or transitional phase. | CT: Portal or delayed phase  
MRI-ECA: Portal or delayed phase  
MRI-Gadoxetate: Portal or transitional |

- CT and MRI
- diagnostic
- features of
- LR-M lesion

<table>
<thead>
<tr>
<th>LR-M Imaging Feature</th>
<th>Definition</th>
<th>CT Example</th>
<th>MRI Example</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Targetoid dynamic enhancement</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rim arterial phase hyperenhancement (APHE)</td>
<td>Spatially defined subtype of APHE in which arterial phase enhancement is most pronounced in observation periphery</td>
<td><img src="image1" alt="CT Example" /></td>
<td><img src="image2" alt="MRI Example" /></td>
</tr>
<tr>
<td>Peripheral washout appearance</td>
<td>Spatially defined subtype of &quot;washout&quot; in which apparent washout is most pronounced in observation periphery</td>
<td><img src="image3" alt="CT Example" /></td>
<td><img src="image4" alt="MRI Example" /></td>
</tr>
<tr>
<td>Delayed central enhancement</td>
<td>Central area of progressive postarterial phase enhancement</td>
<td><img src="image5" alt="CT Example" /></td>
<td><img src="image6" alt="MRI Example" /></td>
</tr>
</tbody>
</table>

| **Targetoid appearance on diffusion-weighted imaging (DWI) or transitional phase (TP)/hepatobiliary phase (HBP)** | | | |
|---------------------------------------------------------------|---------------------------------------------------------------|---------------------------------------------------------------|
| Targetoid restriction | Concentric pattern on DWI characterized by restricted diffusion in observation periphery with less restricted diffusion in observation center | ![DWI B=800](image7) | ![ADC](image8) |
| Targetoid TP or HBP appearance | Concentric pattern in TP or HBP characterized by moderate-to-marked hypointensity in observation periphery with milder hypointensity in center | ![TP](image9) | ![HBP](image10) |
Below are management suggestions by AASLD and LI-RADS in consensus.

**Untreated observations**

- **Multiphase CT or MRI**
  - **No observation**
  - **Categorize each untreated observation detected**
    - **Negative**
      - Return to surveillance in 6 months
    - **LR-NC**
      - Repeat or alternative diagnostic imaging in ≤3 months
    - **LR-1**
      - Return to surveillance in 6 months
      - Consider repeat diagnostic imaging in 6 months
    - **LR-2**
      - Repeat or alternative diagnostic imaging in 3-6 months
    - **LR-3**
      - Repeat or alternative diagnostic imaging in 6 months
    - **LR-4**
      - Multi-disciplinary discussion for tailored workup
      - May include biopsy
    - **LR-5**
      - HCC confirmed
      - Multi-disciplinary discussion for consensus management
    - **LR-M**
      - Multi-disciplinary discussion for tailored workup
      - Often includes biopsy
    - **LR-TIV**
      - Multi-disciplinary discussion for tailored workup
      - May include biopsy

- **If biopsy**
  - Pathology diagnosis
Early diagnosis in HCC:

What to do with LR-4 lesions: Follow, biopsy or treat?
Accuracy of the LIRAD System in CT and MRI Image Analysis of HCC or Overall Malignancy—A Systematic Review

Christian B. van der Pol, Christopher S. Lim, Claude B. Sirlin, Trevor A. McGrath, Jean-Paul Salameh, Mustafa R. Bashir, An Tang, Amit G. Singal, Andreu F. Costa, Kathryn Fowler, Matthew D.F. McInnes

Gastroenterology Volume 156 Issue 4 Pages 976-986 (March 2019)
Cumulative incidence of progression of LR-4 to LR-5 or LR-M is 25%, 32%, 44%, and 46% at 3 months, 6 months, 1 year, and 2 years.

Hong et al. Longitudinal evolution of CT and MRI LI-RADS v2014 Category 1, 2, 3, and 4 observations. Eur Radiol. 2019 Sep:29(9)
Optimal management of LR-4 lesions should be based on MDT discussion:

- Clinical decision making is impacted by several factors including the size (transplant T2 criteria), biomarkers, resection or transplant candidacy, age:
  - watchful waiting? To what extent we change prognosis by waiting? Risk of rapid progression…
  - Repeat testing with mRI (add T2 weighted) if CT was the original study
  - Wait 2-3 months and repeat imaging (downgrade in LR category up to 13% ) [Hong et al. Eur Radiol 2019]
  - Over-treatment approach? With resection or locoregional RX (if not surg/TXP candidate)
  - Risk of non-diagnostic biopsy?
Roles of MDT: How to assess radiological response to TACE and TARE?

• The most used radiologic criteria of response are based either on the measurement of tumor whole (RECIST 1.1) or of its viable portion (mRECIST).
• Response Evaluation Criteria in Solid Tumors (RECIST)
## How to assess for response to LRT?

### Step 1. Apply LI-RADS® CT/MRI Treatment Response Algorithm

### CT/MRI Treatment Response Table

<table>
<thead>
<tr>
<th>Response Category</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>LR-TR Nonviable</td>
<td>- No lesional enhancement OR&lt;br&gt;- Treatment-specific expected enhancement pattern</td>
</tr>
<tr>
<td>LR-TR Equivocal</td>
<td>Enhancement atypical for treatment-specific expected enhancement pattern and not meeting criteria for probably or definitely viable</td>
</tr>
<tr>
<td>LR-TR Viable</td>
<td>Nodular, masslike, or thick irregular tissue in or along the treated lesion with any of the following:&lt;br&gt;- Arterial phase hyperenhancement OR&lt;br&gt;- Washout appearance OR&lt;br&gt;- Enhancement similar to pretreatment</td>
</tr>
</tbody>
</table>
Step 2. Measure Viable Tumor Size

How to measure thick irregular viable tumor

Size of equivocally, probably, or definitely viable tumor

Longest dimension through enhancing area of treated lesion, not traversing nonenhancing area
Interpretation of liver imaging following HCC treatment can be challenging:

- **TACE**: lipiodol retention artifact on CT after a C-TACE, MRI can be used. Radiopaque embolic material is not usually used for DEB-TACE, and the enhancement of viable tumor is not obscured on CT or MRI.

- **TARE or Y90**: is based on micro embolic strategy, response is delayed, response can be visualized after several (6) months (can have persistent hypervascularity despite a response).

- **Stereotactic body radiotherapy (SBRT)**: After SBRT, tumor size and enhancement may transiently increase during the first weeks posttreatment. This phenomenon, called pseudoprogression, has not been described with TARE.

- Response to LR therapy matters, impacts sequence of treatment (switch to systemic therapy earlier! Or use second line therapy if already on systemic therapy track.
Paradigm Change in BCLC B and C HCC: “treatment stage migration”

PR Galle et al. Modified BCLC staging system: 2018
Current BCLC system defines stage B based on:
1) CP score 5-9
2) tumors beyond Milan criteria

Can be a single tumor >5 cm (~over 10 cm) or multiple nodules ≥ 4 (~10-20 bilobar tumors)

Subclassification of BCLC-B:
- Bolondi’s classification in 2012
- Kinki’s classification (Kudo et al., 2015) (modified Bolondi’s)
# BCLC-B subclassification

## Table 2. Subgrouping and treatment indication for patients with intermediate HCC

<table>
<thead>
<tr>
<th>BCLC substage</th>
<th>B1</th>
<th>B2</th>
<th>B3</th>
<th>B4</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT score</td>
<td>5–6–7</td>
<td>5–6</td>
<td>7</td>
<td>8–9</td>
</tr>
<tr>
<td>Beyond Milan and within up-to-7</td>
<td>IN</td>
<td>OUT</td>
<td>OUT</td>
<td>ANY</td>
</tr>
<tr>
<td>ECOG (tumor-related) PS</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0–1</td>
</tr>
<tr>
<td>PVT</td>
<td>NO</td>
<td>NO</td>
<td>NO</td>
<td>NO</td>
</tr>
<tr>
<td>1st option</td>
<td>TACE</td>
<td>TACE or TARE</td>
<td>Research trials</td>
<td>BSC</td>
</tr>
<tr>
<td>Alternative</td>
<td>LT</td>
<td>SOR</td>
<td>TACE</td>
<td>LT</td>
</tr>
<tr>
<td></td>
<td>TACE + ablation</td>
<td>SOR</td>
<td>SOR</td>
<td></td>
</tr>
</tbody>
</table>

TARE = Transarterial radioembolization; SOR = sorafenib. Bolondi et al. [12].

## Table 3. Subclassification and treatment strategy of intermediate-stage HCC (modified Bolondi)

<table>
<thead>
<tr>
<th>BCLC substage</th>
<th>B1</th>
<th>B2</th>
<th>B3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Child-Pugh score</td>
<td>5–7</td>
<td>5–7</td>
<td>8, 9</td>
</tr>
<tr>
<td>Beyond Milan and within up-to-7</td>
<td>IN</td>
<td>OUT</td>
<td></td>
</tr>
</tbody>
</table>

IN

OUT

B3-a

B3-b

<table>
<thead>
<tr>
<th>Concept of treatment strategy</th>
<th>Curative intent</th>
<th>Non-curative, palliative</th>
<th>Curative intent if within up-to-7</th>
<th>Palliative, no treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sub-substage</td>
<td>B3-a</td>
<td>B3-b</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
The presence of portal vein tumor thrombus (PVTT) is considered a strong negative prognostic factor, due to the high recurrence risk.

**Classification of PVTT:**

- VP 1
- VP 2
- VP 3
- VP 4

In contrast to TACE, for which PVTT is a technical issue and a contraindication in case of Vp3-4 stage due to the increased risk of liver ischemic necrosis and treatment-related death, Y90 can be performed in patients with PVTT without major concerns, due to the minimal embolic effect of 90Y-glass microspheres and consequent lower risk of liver ischemia.

Role of SIRT (selective internal radiation therapy) or Y90 TheraSpheres in BCLC B and C stages

stage shift: right-to-left

- Downstaging to resection (multifocal tumors with or W/O portal vein invasion)

- Downstaging to transplant in pts outside the UNOS-DS criteria (according to size or presence of vascular invasion)

- Providing a durable local tumor control in unresectable or non-transplant candidates
Surgical resection of locally advanced HCC

The ideal candidate for surgical resection according to the BCLC staging system:

- Single tumor
- Tumor size < 5 cm
- No vascular invasion
- => 40% liver remnant in cirrhotics

Can we expand the surgical resection eligibility to BCLC-B or C stages?
Downstaging to surgery with SIRT/Y90:

- Radioembolization with high dose personalized dosimetry improves outcomes for patients with advanced HCC

**THE LANCET**

*Gastroenterology & Hepatology*

*Volume 6, Issue 1, January 2021, Pages 17-29*

**Articles**

Personalised versus standard dosimetry approach of selective internal radiation therapy in patients with locally advanced hepatocellular carcinoma (DOSISPHERE-01): a randomised, multicentre, open-label phase 2 trial

*Prof Etienne Garin MD a, b, 1, 2, R, E, Lambros Tselikas MD a, Prof Boris Guliu MD 1, Julia Chalaye MD 1, Julien Edeline MD a, b, Prof Thierry de Baere MD 1, Prof Eric Assenat MD 1, Vania Tacher MD 1, Corentin Robert MD a, Marie Terroir-Cassou-Mounat MD 1, Prof Denis Mariano-Goulart MD 1, 2, Giuliana Amaddeo MD 1, Xavier Palard MD a, b, Antoine Hollebecque MD 1, Marlyne Kafrouni PhD 1, Helène Regnault MD 1, 2, Prof Karim Boudjema MD a, b, Serina Grimaldi MD 1, ... Milan Milliner*
Downstaging to surgery with SIRT/Y90:

- The first randomized, multicenter, prospective study to compare personalized dosimetry and standard dosimetry in patients with hepatocellular carcinoma in patients with locally advanced hepatocellular carcinoma.
- 75% of pts BCLC-C with tumor in vein (PVT)
- Mean index tumor size ~ 10 cm
- Majority of pts had unilobar disease with some bilobar disease

- 31 pts with Personalized Dosimetry (PD): =>205 Gy to the index tumor
- 29 pts with Standard Dosimetry (SD): 120 +/- 20 Gy to the perfused liver
Dose-response correlation:

• Higher Objective Response rate (ORR) with PD:
  -77% for index tumor with TD=> 205 Gy
  -22% for index tumor with TD <205 Gy

• No increased complication/toxicity rates in PD vs. SD

• Post-Y90 resection:
  -35% of pts in PD group underwent surgery (44% had PVT)
  -4% of pts in SD group underwent surgery (0% with PVT)
Personalized dosimetry strongly increases OS in selected BCLC-C pts

26.6 mo in the PD arm (>205 Gy) vs. 10.7 mo in SD arm(<205 Gy) (p=0.0096)
LEGACY study (excellent outcome from SIRT in large unresectable unifocal HCC)

- FDA approved Y-90 for the treatment of unresectable HCC in March 2021.
- Retrospective, single-arm, multi-center study (3 sites) that enrolled patients with early and advanced HCC between 2014-2017.
• High dose dosimetry was used; median absorbed dose to the treated liver volume was 410 Gy.

• ORR: 88.3% (duration of Rx =>6 mos)

• 3-yr OS: 86.6% for all pts
• 92% for those neoadjuvant patients resected or transplanted.
Swimmer plot of time to response and duration of response by localized mRECIST (confirmed response).

Solitary tumors up to 8 cm
(Median tumor size 2.7 cm)
N=162
Median FU: 29.9 mos
Downstaging to liver transplant (LT) criteria with SIRT

- UNOS-UCSF downstaging protocol for LT eligibility:
  - Inclusion criteria –
    - 1 lesion >5 cm and ≤8 cm
    - 2 or 3 lesions ≤5 cm w/ total tumor diameter ≤8 cm
    - 4 or 5 lesions ≤3 cm w/ total tumor diameter ≤8 cm
    - No vascular invasion on imaging
  - Require 6-mo waittime on the transplant list to receive HCC MELD exception

Recent UNOS Policy Change
stage shift: right-to-left

- Patients initially beyond UCSF/UNOS-DS ("all-comers") can be considered for MELD exception on a case-by-case basis

- Difficult to maintain All-comers within Milan Criteria during the waittime (high dropout rate)

- Patient selection is important (low AFP level)
Downstaging to transplant criteria with SIRT
(Mazzaferro, V. et al. – Lancet Oncol, 21 July 2020)

- the first prospective, randomized, controlled trial to explore the benefit of liver transplantation in patients who achieved successful and sustained downstaging of hepatocellular carcinomas exceeding the Milan criteria.
- small study: ~20 in each arm but long FU (median 71 mos)
- 2011-2015
• 9 Italian transplantation centers

• absence of macrovascular invasion or extrahepatic spread

• underwent tumor downstaging with locoregional, surgical, or systemic therapies according to multidisciplinary decision

• After an observation period of 3 months, patients with partial or complete responses were randomly assigned (1:1).
• 50% met UCSF criteria
• Sum of the tumors: 79.0 mm (70.5–95.5)

• 5-year OS was 77.5% in the transplantation group versus 31.2% in the control group (HR 0.32, 95% CI 0.11–0.92; p=0.035).

• Trial closed early
OLT for HCC with PVTT
“stage shift: right-to-left”

- Multicenter retrospective study, 11 US and EU centers, N= 30 pts
- HCC stage T3 (no Vp4)
- Downstaged and transplanted

- At the time of vascular invasion diagnosis, 14 patients (46.7%) had a multifocal HCC, and the median diameter of the largest HCC nodule was 5.9 cm (range: 2–15)
5 yr OS 60%

Predictors of HCC recurrence (26.7% of pts):
- AFP > 10 at the time of OLT (recurrence rate: 50% vs. 11%)
- Explant tumor characteristics: number of viable nodules, presence of residual HCC, satellite nodules
  - > Milan criteria
HCC stage migration left-to-right: B→ C/D

Early initiation of systemic therapy in intermediate stage

Updated treatment recommendations for hepatocellular carcinoma (HCC) from the ESMO Clinical Practice Guidelines A. Vogel, E. Martinelli, on behalf of the ESMO Guidelines Committee

Candidates:
-Not suitable for local RX: multifocal and bilobar disease
-TACE refractory (needs to be further defined)
Use of systemic therapy in Child-Pugh B patients

- Significant unmet need for prospective data in CP-B HCC pts
- Challenges:
  - Heterogeneity within the CP-B status (ascites and encephalopathy as subjective measures)
  - Overall poor prognosis related to the underlying CP-B status (affects PFS)
  - Poor tolerability and increased adverse events in CP-B
  - Trials enroll CP A pts
  - Long-term real-world data supports the safety and tolerability of Sorafenib in CP-B (with reduced OS in CP-B)

Use of systemic therapy in Child-Pugh B patients

Based on CheckMate 040 phase 1/2 trial results, NCCN (National Comprehensive Cancer Network) recommends the use of Nivolumab in pts with CP-A and B7.

Recent post-hoc analysis of REFLECT study on safety and efficacy of Lenvatinib use in pts with liver decompensation [despite the drop in ORR, pts may continue to see benefits from LEN]

Huynh, et al., Poster Presentation Abstract #298, ASCO-GI (virtual meeting) Jan 15-17, 2021
Patient selection for systemic therapy

- 1st line treatment in advanced HCC: Atezolizumab and Bevacizumab
- Bev is an anti-VEGF, inhibits endothelial integrity leading to risk of bleeding
- Single agent Bevacizumab had 10-20% variceal bleeding rate in earlier studies
- **Does every pt need an EGD prior to Rx based on IMBRAVE 150 trial?**

Can we use Baveno VI classification for risk stratification of varices? **Not validated in advanced HCC pts**

AASLD practice Guideline 2017: patients with a LS <20 kPa on transient elastography and PLT count > 150,000/mm3 have a very low probability (<5%) of having high-risk varices, and EGD can be avoided.

Need real world data and MDT discussion

Paradigm change in systemic therapy: MDT to enroll pts in ongoing phase III trials in HCC
Take away points

- MDT can improve patient outcome by developing personalized treatment plans given multiple areas of uncertainty in guidelines.
- BCLC-B includes a heterogeneous group of HCC patients who would be candidates for OLT, TACE, Y90, or even systemic therapy [not one size fits all], consider stage migration
- Expansion of resection eligibility with SIRT? (Guidelines need to be amended)
- Personalizing approach to SIRT (Dosimetry and boosting radiation)
- Intention to downstage pts to OLT criteria should be assessed throughout the spectrum of HCC stages
- Hepatologists can play a strong role on the management of HCC
Case presentation: multifocal unilobar HCC

- 67 Y/O gentleman with hx of regular alcohol use presented with abdominal pain, found to be positive for HCV with a high VL and a large liver mass in the right lobe plus a smaller satellite lesion on a background nodular liver.
- AFP 9
- Bili 0.5
- PLT 233
- No ascites, EGD with no varices
- ECOG 0
Heterogenous enhancement of an 11-cm seg 8 mass with central scarring
Targeted biopsy confirmed a well-diff HCC
Satellite small lesion adjacent to the index tumor
What would be the best management plan?

- Systemic therapy with 1\textsuperscript{st} line Atezo/Bev
- Surgical resection
- Y90 radioembolization
- Treat with DAAs first, then refer for radioembolization once HCV is undetectable
- Best supportive care
Case continues:

- Pt underwent Y90
- Started DAA after the Y90 administration
- Follow up MRI at 3 months showed viable residual tumor, received 2\textsuperscript{nd} round of Y90
- Follow up CT at 5 months continued to show residual viable tumor
- Started on Sorafenib and referred to MDT
&-month follow up MRI discussed at tumor board

- Left lobe hypertrophy
- Seg 8 lesion with heterogenous enhancement c/w residual tumor, decreased in overall size
- No pulmonary nodule or positive LN, satellite lesion with complete response
s/p right lobe resection 9 mo after the initial Y90

- Path showed vascular invasion
- Tumor size: 11.8 cm with >30% viable HCC

- Follow up MRI 2.5 years post resection with no tumor recurrence (PFS)
- No liver decompensation
Thank you!