What a center needs to manage a patient with hepatocellular carcinoma

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Il sottoscritto dichiara di aver avuto negli ultimi 12 mesi conflitto d’interesse in relazione a questa presentazione:

**Grant and research support:** BMS, Gilead Science

**Advisory committees:** Merck, Roche, Novartis, Bayer, BMS, Gilead Science, Tibotec, Vertex, Janssen Cilag, Achillion, Lundbeck

**Speaking and teaching:** Tibotec, Roche, Novartis, Bayer, BMS, Gilead Science, Vertex

che la presentazione non contiene discussione di farmaci in studio o ad uso off-label.
Hepatocellular Carcinoma: Distinct Features

1. The tumor develops in the context of well-known environmental risk factors. The dominant role of HBV and HCV.

2. The tumor is strictly associated with chronic liver disease, mainly cirrhosis.

3. One of the few cancers not requiring histology for diagnosis in all cases. Radiological diagnosis possible in cirrhotics and HBV patients.

4. The sole solid cancer treatable by organ transplantation.
Changes in Age-adjusted Mortality Rates in Men from Primary Liver Cancer by European Country from 2000 to 2010

Bertuccio et al, Annals of Oncology in press
### The Changing Scenario of HCC Over the Last Two Decades in Italy

<table>
<thead>
<tr>
<th>Data set</th>
<th>3027 HCCs seen consecutively from 1987 to 2008</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sites</td>
<td>11 centers in Italy (ITALICA)</td>
</tr>
</tbody>
</table>

#### Major Findings
- Progressive patient ageing
- Recent increase in alcoholic etiology
- Increasing incidence vs symptomatic diagnosis
- Favourable tumor stage migration

*Santi et al, J Hepatol 2012;56:397-405*
Steps in HCC Clinical Decision-making

- Screening
- Detection
- Characterization-diagnosis
- Staging (outcome prediction)
- Treatment indication (prognosis refined)
AISF Algorithm for Investigation of Small Nodules Found On Screening in Patients with Cirrhosis

Liver nodule

< 1 cm

Reapeat US at 3 months

Growing/changing character

Investigate according to size

Stable

> 1 cm

4 – phase MDCT/dynamic Contrast enhanced MRI or CEUS

Arterial hypervascularity and venous or delayed phase washout

Yes

Other contrast enhanced Study

HCC

Arterial hypervascularity and venous or delayed phase washout

Yes

Biopsy

No

No

Yes

Bolondi et al, Dig Liver Dis in press.
Management of HCC in the General Hospitals in Italy

Prospective study (2008-2010) 30 hospitals, Italy

424 patients with a de-novo HCC in cirrhosis

220 (52%) had a < 3cm tumor

Radiological diagnosis of HCC

- 93% CT scan
- 62% CE-US
- 17% MRI

Borzio et al, AASLD, Oct.2, 2010, abs # 1769
# The Importance of Liver Biopsy to Discriminate HGDN from Early HCC

<table>
<thead>
<tr>
<th>Diagnostic approach</th>
<th>Etiology</th>
<th>HGDN vs HCC</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histology</td>
<td>Reticulin</td>
<td>HBV/HCV</td>
<td>Kojiro et al 2005</td>
</tr>
<tr>
<td>Immunostain</td>
<td>GPC3, HSP70 GS, CHC</td>
<td>Mixed</td>
<td>At least 2: 50% sens. 100% spec.</td>
</tr>
<tr>
<td>PCR</td>
<td>13 genes GPC-3, survivin LYVE-1</td>
<td>Mixed</td>
<td>98% accuracy 94% accuracy</td>
</tr>
<tr>
<td>Microarray</td>
<td>120 genes 93 genes</td>
<td>HBV HCV</td>
<td>100% accuracy</td>
</tr>
</tbody>
</table>
Study follow-up: 6.1 yr

Highly compliant patients in a near optimal setting

**692 (69%)** had consistent surveillance. Study site was the predictor

**83 HCC (28%)** detected beyond Milan criteria

- 3 (13%) due to absence of screening
- 4 (17%) due to absence of follow-up
- 16 (70%) due to absence of detection

*Singal et al, Am J Gastroenterol 2013, in press*
**EASL: BCLC Staging System and Treatment Strategy**

**Stage 0**
- **PST 0, child-Pugh A**
  - **Very early stage (0)**
    - Single <2cm, Carcinoma in situ
      - Single
        - Portal pressure/bilirubin
          - Increased
            - Associated diseases
              - Yes
                - TACE
              - No
                - Resection
          - Normal
            - OLT
  - **Terminal stage (D)**

**Stage A-C**
- **PST 0-2, child-Pugh A-B**
  - **Early stage (A)**
    - Single or 3 nodules ≤ 3 cm
      - 3 nodules ≤ 3cm
        - Portal invasion
          - N1, M1, PS 1-2
            - Sorafenib
          - PS 0
            - RF/PEI
  - **Intermediate stage (B)**
    - Multinodular PS 0
      - TACE
  - **Advanced stage (C)**
    - Portal invasion N1, M1, PS 1-2
      - Sorafenib
  - **Target: 40%**

**Stage D**
- **PST >2, child-Pugh C**
  - **Terminal stage (D)**
    - Best supportive care
  - **Target: 10%**

**Curative treatment (30-40%)**
- **Target: 20%**

Is Portal Hypertension a Contraindication to Hepatic Resection? Single Tumor in Child-Pugh A

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>No Patients</th>
<th>Five Year Survival</th>
<th>PHT (+)</th>
<th>PHT (-)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capussotti¹</td>
<td>Italy</td>
<td>217</td>
<td></td>
<td>52%</td>
<td>62%</td>
<td>0.008</td>
</tr>
<tr>
<td>Ishizawa²</td>
<td>Japan</td>
<td>272</td>
<td></td>
<td>56%</td>
<td>71%</td>
<td>0.008</td>
</tr>
<tr>
<td>Cucchetti³</td>
<td>Italy</td>
<td>156</td>
<td></td>
<td>37%</td>
<td>64%</td>
<td>0.008</td>
</tr>
</tbody>
</table>

Management of HCC in the General Hospitals in Italy

Prospective study (2008-2010) 30 hospitals, Italy
424 patients with a de-novo HCC in cirrhosis
220 (52%) had a < 3cm tumor

Radiological diagnosis of HCC
93% CT scan
62% CE-US
17% MRI

35% of early HCC received non curative therapies

Borzi et al, AASLD, Oct.2 2010, abs # 1769
### Incidence and Treatment of HCC in a Referral Center
(AM & A Migliavacca Liver Center, Milan)

<table>
<thead>
<tr>
<th>Year</th>
<th>Newly Diagnosed vs Total HCC</th>
<th>BCLC 0/A</th>
<th>Non Curative Treatments *</th>
</tr>
</thead>
<tbody>
<tr>
<td>2011</td>
<td>50/399 (13%)</td>
<td>42 (84%)</td>
<td>14/42 (33%)</td>
</tr>
<tr>
<td>2012</td>
<td>60/410 (15%)</td>
<td>42 (70%)</td>
<td>20/42 (48%)</td>
</tr>
<tr>
<td>Total</td>
<td>110/809 (14%)</td>
<td>84 (76%)</td>
<td>34/84 (40%)</td>
</tr>
</tbody>
</table>

* Causes: advanced age (n=9, 11%), co-morbidities (n=5, 6%), strategic location (n=20, 24%)

Sangiovanni & Iavarone, unpublished
## Association of Multidisciplinary (MDC) HCC Clinic with Clinical Outcome

105 patients diagnosed after the MDC clinic (2010) vs 209 patients diagnosed in the 3 previous years

<table>
<thead>
<tr>
<th>Comparison</th>
<th>MDC Clinic</th>
<th>Previous Years</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Received treatment</td>
<td>56%</td>
<td>44%</td>
<td>0.04</td>
</tr>
<tr>
<td>2. Time to treatment (mo.)</td>
<td>2.2</td>
<td>4.7</td>
<td>0.001</td>
</tr>
<tr>
<td>3. Survival time (mo.)</td>
<td>15.2</td>
<td>4.7</td>
<td>0.002</td>
</tr>
<tr>
<td>4. One-year survival</td>
<td>64%</td>
<td>47%</td>
<td>0.001*</td>
</tr>
</tbody>
</table>

*after excluding BCLC-D patients

Yopp et al, Journal of Clinical Oncology 2013;31 suppl:332
Management of Hepatocellular Carcinoma Requires a Multidisciplinary Approach

Hepatology/Oncology

Radiology/Pathology

Interventional Radiology

Hepatobiliary Surgery

Liver Transplant Program