9th Liver Interest Group Annual Meeting

HCC guidance

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Introduction

• Most common primary hepatic malignancy
• Annual incidence of 782000*
• Globally accounts for 9.2% of all new cancer cases
• 5th most common cancer in males and 8th in females
• Around 84% occur in less developed regions
• Annual mortality is 746000*
• Worldwide it is the second leading cause of cancer-related death

• Addressing key questions
• Assessment of level of evidence
• Grade of recommendations

• Prevention strategies
• Diagnostic algorithms
• Treatment algorithms
Prevention strategies

Primary prevention

• HBV vaccination: birth dose, high risk groups
• Safe injection and transfusion practices
• Decrease toxin exposure (Aflatoxin B1)
• Education on risk factors
• Control of obesity, diabetes and NAFLD
• Management of iron overload
• Limit alcohol ingestion
• Treatment for HBV and HCV

Secondary prevention

• Screening for and surveillance of high-risk populations

Tertiary prevention

• Follow-up of treated patients especially HBV-infected and cirrhotic patients
Prerequisites for surveillance

- disease with high prevalence, mortality and morbidity
- effective therapies should be available
- the at-risk population must be readily identifiable
- screening tests - sensitive and specific, minimally invasive, widely available and inexpensive
- treatment of occult disease should offer advantages compared to treatment of symptomatic disease
- surveillance program with effective recall procedures
- screening need must be sanctioned by healthcare providers and accepted by patients
At-risk population

Surveillance has been found to be cost-effective in

• Cirrhotics*
  – prevalence of cirrhosis in HCC patients is 85%-95%
  – HCC incidence rate 2-4% per year (threshold ≥1.5%/year)

• Chronic hepatitis B
  substantial differences in guidelines on subgroups based on clinical and ethnic criteria

• Stage 3 fibrosis or advanced/bridging fibrosis

*Child-Pugh C - only if on transplant list
Screening tests

• Ultrasound
  • sensitivity of 93 % (63% for early stage HCC)
• AFP
  • 10-11 ng/ml - sensitivity 80%; specificity 70%
  • 17-21 ng/ml - sensitivity 65%; specificity 85%
  • ≥20 ng/ml- sensitivity 41-65%; specificity 80%-94%
• Combination of AFP and Ultrasound
  • AFP increase ≥2 times from 12 month nadir and US
    - sensitivity 99.2%; specificity 71.5%
Screening interval

• 6 versus 12 monthly US (meta-analyses)
  – significantly higher sensitivity with 6 monthly for detecting early HCC

• 3 versus 6 monthly (randomized controlled trial)
  – no difference in HCC incidence (p=0.13) or in prevalence of tumours ≤30 mm in diameter (p=0.30) was seen
However, the clinical usefulness of such analyses has not been proven and has not entered routine diagnostics, so far. Molecular markers have been assessed on HCC tissues for their predictive potential and have been used as inclusion criteria in clinical trials. As the number of clinical trials increases, the availability of HCC tissue has become more relevant for including patients. Although always an individual decision integrating clinical (palliative vs. curative) and patient specific factors (age, etc.), several centres have introduced more active biopsy strategies into their policies.

Potential risks of liver tumour biopsy are bleeding and needle track seeding. In a meta-analysis, the risk of tumour seeding after liver biopsy was reported to be 2.7% with a median time interval between biopsy and seeding of 17 months, but this study probably suffers from publication bias and even lower rates are expected in experienced centres. It has further been reported that needle track seeding can be treated well, e.g. by excision or radiation and does not affect outcome of oncological treatment.

In a meta-analysis of the bleeding risk of liver tumour biopsies, mild bleeding complications range around 3–4%, while severe bleeding complications requiring transfusions are reported in 0.5% of cases. In conclusion, it is now widely accepted that the potential risks, bleeding and needle track seeding, are infrequent, manageable and do not affect the course of the disease or overall survival. In general, they should not be seen as a reason to abstain from diagnostic liver biopsy.

Synthesis of radiological and histopathological diagnosis/synopsis

Diagnostic assessment of hepatic lesions suspected of being HCC in a specific patient is influenced by the size and location of the lesion, the state of the non-tumourous liver, the clinical status of the patient, the imaging patterns, the expertise of the diagnostic physicians, the extent of therapeutic options, and general conditions of the respective healthcare system. Generally proposed diagnostic algorithms may not be able to address all parameters. The certainty of diagnosis represents a high priority; its impact is rising with extent and effectiveness of therapy in HCC and its differential diagnoses.

In cirrhotic patients, the diagnosis of HCC is often based on contrast-enhanced imaging as shown in the diagnostic algorithm (Fig. 2). Biopsy of the lesion is indicated when the imaging-based diagnosis remains inconclusive, especially in lesions smaller than 2 cm in diameter where the diagnostic performance of contrast-enhanced imaging is lower. Considering a degree of uncertainty with imaging-based HCC diagnosis (around 5–10%), even when classical diagnostic parameters are fulfilled, biopsy has to be considered if a higher level of certainty is required. Furthermore, several centres have introduced Mass/nodule at imaging

- <1 cm
  - Repeat US at 4 mo
  - Stable****
  - Growing/changing pattern
  - Biopsy unclear: Consider re-biopsy

- >1 cm
  - Multiphasic contrast-enhanced CT, or multiphasic contrast-enhanced MRI*, or gadoxetic-enhanced MRI**
  - 1 positive technique: HCC imaging hallmarks
  - No Yes
  - Use the other modality multiphasic contrast-enhanced CT, or multiphasic contrast-enhanced MRI*, or gadoxetic-enhanced MRI**, or contrast-enhanced ultrasound***
  - 1 positive technique: HCC imaging hallmarks
  - No Yes
  - Biopsy
  - - Non-HCC malignancy
  - - Benign
  - HCC
Efficacy of HCC surveillance

HCC surveillance is associated with improved

• **Early stage detection**
  
  70.9% vs 29.9% if diagnosed incidentally or if presenting with symptoms

• **Curative treatment rates**
  
  51.3% vs. 23.8% if diagnosed incidentally or if presenting with symptoms

• **Significantly prolonged survival**
  
  50.8% vs. 28.2% 3-year survival if diagnosed incidentally or if presenting with symptoms

Treatment strategy

### Prognostic stage

**Very early stage (0)**
- Single <2 cm
- Preserved liver function¹, PS 0

**Early stage (A)**
- Single or 2-3 nodules <3 cm
- Preserved liver function¹, PS 0

**Intermediate stage (B)**
- Multinodular, unresectable
- Preserved liver function¹, PS 0

**Advanced stage (C)**
- Portal invasion/extrahepatic spread
- Preserved liver function¹, PS 1²-2

**Terminal stage (D)**
- Not transplantable HCC
- End-stage liver function

### Treatment

- **Ablation**
- **Resection**
- **Transplant**
- **Chemoembolization**
- **Systemic therapy²**
- **BSC**

### Survival

- >5 years
- >2.5 years
- ≥10 months
- 3 months

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¹ Includes Child-Pugh A patients without ascites.
² Performance status 0-1.
³ For tumours ≤2 cm.
⁴ Includes sorafenib, regorafenib, axitinib.
⁵ Includes bevacizumab, sunitinib, cabozantinib.
Prognosis of untreated HCC

Median survival as per Barcelona Clinic Liver Cancer (BCLC) stage

- Stages 0/A  13.4 months
- Stages B   9.5 months
- Stages C   3.4 months
- Stages D   1.6 months
Prognosis of treated HCC

• Liver resection* >70% 5 year survival
• Local ablation* >70% 5 year survival
• Transplantation* >75% 5 year survival
• TACE 20 mo improved survival
• Sorafenib 2.9 mo improved survival

*Treated within the Barcelona criteria

Llovet JM, Bruix J. Hepatology 2003;37:429–42
Guidance in sub-Saharan Africa

• Current guidelines are exclusively based on data from well-resourced countries and are tailored for the disease spectrum as seen in these populations.

• Assume that medicine is practiced in a standard well-resourced environment and that imaging and treatment options are generally available.
HCC in sub-Saharan Africa

• Annual incidence 103.8 per 100 000 vs. 1 - 7 per 100 000
• Male predominance 8:1 vs. 2.5:1
• Mean age of onset 33.4 - 47.5 years vs. 60 - 80 years
• Present more often with tumour-related symptoms
• Present more often with complicated disease
• More rapid tumour growth and larger tumour burdens
• Very low resectability rates
Is it a different disease?
Epidemiology

• In order of prevalence
  1. Western Africa
  2. Central Africa
  3. Eastern Africa
  4. Southern Africa

• Incidences >20/100,000 inhabitants reported in a number of African Countries
Characteristics, management, and outcomes of patients with hepatocellular carcinoma in Africa: a multicountry observational study from the Africa Liver Cancer Consortium

2566 patients
21 referral centres

Published Online December 2, 2016 http://dx.doi.org/10.1016/S2468-1253(16)30161-3
## BCLC stage at presentation

<table>
<thead>
<tr>
<th>BCLC stage</th>
<th>Sub-Saharan Africa*</th>
<th>Europe**</th>
</tr>
</thead>
<tbody>
<tr>
<td>A-B</td>
<td>5%</td>
<td>40.4%</td>
</tr>
<tr>
<td>C</td>
<td>23%</td>
<td>43.9%</td>
</tr>
<tr>
<td>D</td>
<td>72%</td>
<td>14.5%</td>
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</table>

### Treatment in sub-Saharan Africa

$n=1315$

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Count (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Curative treatment</strong></td>
<td></td>
</tr>
<tr>
<td>Resection</td>
<td>8 (&lt;1%)</td>
</tr>
<tr>
<td>Local ablation</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Transplantation</td>
<td>0 (0%)</td>
</tr>
<tr>
<td><strong>Palliative</strong></td>
<td></td>
</tr>
<tr>
<td>TACE</td>
<td>5 (&lt;1%)</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>12 (&lt;1%)</td>
</tr>
</tbody>
</table>

Screening for HCC when treatment options are not in place is bound to be an expensive failure.
Diagnosis and treatment in sub-Saharan SA

• Online survey
• Questions on diagnostic and treatment resources in public and private facilities
• HPB surgeons at 13 tertiary centres
• Nigeria, Senegal, Ghana, Cameroon, Kenya, Uganda, Namibia, Zimbabwe
Diagnostic tools in SSA

- Alfa-fetoprotein
- Ultrasound
- CT
- MRI
- PET

Legend:
- Public service
- Private service
Treatment in SSA

- Liver resection
- Local ablation
- Transplantation
- TACE
- Sorafenib

Public service vs. Private service
The Lancet Commission on Global Surgery identified Western, Eastern and Central Sub-Saharan Africa respectively as the regions with the highest, second highest and third highest rates of surgical need per population in the world

Resource-sensitive guidelines

Treatment capability

Diagnostic capabilities

Prevention strategies
Minimal resources

• Treatment
  – Best supportive care
  – Referral of early tumours

• Diagnostics
  – Confirming the diagnosis

• Prevention
  – Primary prevention

Medium resources

• Treatment
  – Liver resection
  – Local ablation

• Diagnostics
  – Definitive diagnosis
  – Staging

• Prevention
  – Primary prevention
  – Secondary prevention

High resources

• Treatment
  – International guidelines apply (AASLD/EASL)

• Diagnosis
  – International guidelines apply (AASLD/EASL)

• Prevention
  – Primary
  – Secondary
  – Tertiary

Hepatocellular carcinoma: Exploring the impact of ethnicity on molecular biology

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Research in Africa

Less than 1% of currently ongoing clinical HCC trials are conducted on the continent

Conclusion

• Implementation of resource-sensitive guidance algorithms in sub-Saharan Africa is a realistic and feasible approach.

• However, the endeavour will be eroded by geographical and economic between and within country variations in the quality and accessibility of health care.

• Accounting for, minimizing, or at best eradicating these inequalities will be a prerequisite for the successful implementation of these algorithms.

• These inequalities are a powerful political tool to bring about change and stimulate improvement of health care.
Thank you