Surgical resection for hepatocellular carcinoma (HCC)

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I have nothing to disclose
Introduction

- HCC is the sixth most common neoplasm and the third leading cause of cancer-related death in the world.
- The highest prevalence of this tumor is in Asia and Africa, although during the last decades the prevalence in Western countries in Europe and USA is rising.
- HCC results in between 250,000 and one million deaths globally per annum.
- Almost 80% cases are due to underlying liver cirrhosis (chronic HBV or HCV infection).
- Compensated cirrhosis have a 3-4% annual incidence of HCC, and those with chronic hepatitis have an approximate annual risk of 1%.
- HCC is typically diagnosed late and the median survival following diagnosis is approximately 6-20 months.
### Risk factors for HCC

<table>
<thead>
<tr>
<th>Geographic area</th>
<th>AAIR M/F</th>
<th>Risk factors</th>
<th>Alcohol (%)</th>
<th>Others (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Europe</td>
<td>6.7/2.3</td>
<td>60-70</td>
<td>10-15</td>
<td>20</td>
</tr>
<tr>
<td>Southern</td>
<td>10.5/3.3</td>
<td>10-70</td>
<td>10-15</td>
<td>20</td>
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<tr>
<td>Northern</td>
<td>4.1/1.8</td>
<td>20-50</td>
<td>10-15</td>
<td>20</td>
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<tr>
<td>North America</td>
<td>6.8/2.3</td>
<td>50-70</td>
<td>10-15</td>
<td>20</td>
</tr>
<tr>
<td>Asia and Africa</td>
<td>20</td>
<td>70</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Asia</td>
<td>21.6/8.2</td>
<td>70</td>
<td>10</td>
<td>20</td>
</tr>
<tr>
<td>China</td>
<td>23/9.6</td>
<td>70</td>
<td>10-20</td>
<td>10</td>
</tr>
<tr>
<td>Japan</td>
<td>20.5/7.8</td>
<td>30</td>
<td>10-20</td>
<td>10</td>
</tr>
<tr>
<td>Africa</td>
<td>1.6/5.3</td>
<td>30-70</td>
<td>10-15</td>
<td>20</td>
</tr>
<tr>
<td>WORLD</td>
<td>16/6</td>
<td>31</td>
<td>54</td>
<td>15</td>
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*EASL-EORTC Clinical Guidelines, J Hepatology 2012*
HCC Classification Systems

- TNM – neglects underlying liver disease
- Child-Pugh – neglects TNM
- Okuda – (liver disease + % of liver involvement)
- Barcelona Clinic Liver Cancer (BCLC)
- “Royal Free” HCC scoring
- CLIP (Cancer of the Liver Italian Program)
- Japan Integrated Staging (JIS) score
- Hong Kong Liver Cancer (HKLC)
- ITA.LI.CA
BCLC staging and treatment strategy for HCC

**Stage 0**
- PST 0, Child-Pugh A
  - Very early stage (0)
    - Single <2 cm, Carcinoma in situ
      - Single
        - Portal pressure/bilirubin: Normal
        - Associated diseases: No
          - Resection
        - Associated diseases: Yes
          - Liver transplantation (CLT/LDLT)
  - 3 nodules ≤3 cm
    - Associated diseases: No
      - RF/PEI
    - Associated diseases: Yes
      - TACE

**Stage A-C**
- PST 0-2, Child-Pugh A-B
  - Early stage (A)
    - Single or 3 nodules ≤3 cm, PS 0
      - Single
        - Portal pressure/bilirubin: Increased
          - Associated diseases: No
            - RF/PEI
          - Associated diseases: Yes
            - Sorafenib
      - 3 nodules ≤3 cm
        - Associated diseases: No
          - RF/PEI
        - Associated diseases: Yes
          - Sorafenib

**Stage D**
- PST >2, Child-Pugh C*
  - Intermediate stage (B)
    - Multinodular, PS 0
      - TACE
  - Advanced stage (C)
    - Portal invasion, N1, M1, PS 1-2
      - Sorafenib
  - Terminal stage (D)
    - Best supportive care

**Curative treatment (30-40%)**
- Median OS >60 mo; 5-yr survival: 40-70%

**Target: 20%**
- OS: 20 mo (45-14)

**Target: 40%**
- OS: 11 mo (6-14)

**Target: 10%**
- OS: <3 mo
Hong Kong Liver Cancer (HKLC) Staging System

Yau et al. Gastroenterology 2014
Surgical resection for HCC

- Remains the main pillar in curative treatment of HCC

- Patients **ideally** suited for resection have localized HCC confined to the liver without radiological evidence of invasion of the hepatic vasculature, well preserved hepatic function, and no evidence of portal hypertension

- Thus **only 15-30%** of newly diagnosed patients are potentially resectable

*Llovet et al. Semin Liver Dis 2005*
Chronic liver disease/cirrhosis - problems

- Deterioration of protein synthesis and metabolism
- Gastrointestinal tract congestion, ascites, pancytopenia due to portal hypertension and hypersplenism
- Susceptibility to infectious disease and hepatopulmonary syndrome (hypoxemia) due to increased shunt vessels
- Lower rate of regeneration

High morbidity and mortality following anesthesia and surgery
Multidisciplinary approach is necessary!!!

- Due to complexity of disease:
  - tumor stage
  - liver function
  - physical status (co-morbidity)
Patient evaluation before liver resection

Resection for hepatocellular carcinoma

- Underlying liver disease
  - Fibrosis
    - Liver stiffness measurement
    - Liver biopsy (F0-F4)
  - Inflammation
    - Transaminase level
    - Liver biopsy (A0-A3)
  - Fatty liver disease
    - Liver biopsy (NAS, SAF)

- Liver function
  - ICG R15
    - <10% normal
    - <14% major resections
    - <22% minor resection

- Portal pressure
  - Indirect evaluation
    - Ascites
    - Platelet level
    - Liver/spleen ratio
    - Collateral shunts
    - Esophageal varices
    - Direct HPVG evaluation

- Liver volume
  - FLR:
    - in cirrhosis >40%
    - in chronic hepatitis >30%

Fig. 1. Evaluation of the underlying parenchyma’s status and function. NAS: Non-alcoholic fatty liver disease activity score; SAF: Steatosis, activity, fibrosis; ICG: indocyanine green; PVE: Portal vein embolization; HPVG: Hepatic vein portal vein gradient; CT: Computed tomography; FLR: Future liver remnant; TLV: Total liver volume.

Fan ST J Hepatobiliary Pancreat Sci 2010
Patients selection for resection in chronic liver disease

<table>
<thead>
<tr>
<th>Resection</th>
<th>Criteria</th>
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| Minor     | Child-Pugh A  
           | Bilirubin $\leq 2$ mg/dL  
           | Absence of ascites  
           | Platelets $>100,000$/mm |
| Major     | Criteria for minor resection plus:  
           | Bilirubin $\leq 1$ mg/dL  
           | Absence of portal hypertension  
           | Portal vein embolization for future liver remnant of $<40\%$ |

Truty and Vauthey. Ann Surg Oncol 2010
Surgical resection for HCC - important questions

- Tumor size
- Number of tumors
- Anatomic vs non-anatomic resections
- Resection margin
- Presence of portal hypertension
- Ruptured HCC
- Vascular invasion
- Extrahepatic disease
74-year old patient with chronic hepatitis B
- Diabetes mellitus, slightly impaired kidney function (GFR 45)
- Liver function test normal, AFP 45, bilirubin 11 umol/ml, platelets 300 000/mm³

Referred to tertiary center

US elastography – liver biopsy showed grade 3 fibrosis

CT volumetry – FLR (segment 2,3,1 – FLR/TLV 25%)
- PVE – right PV + segment 4
- control CT volumetry 4 weeks later: FLR 29%
- extended right hemihepatectomy (right trisectionectomy)
HCC resection: tumor size

- size per se is not contraindication for resection, however the size reflects the risk of microvascular invasion and therefore poor outcome
  
  - <2 cm - 20% MVI
  - 2-5 cm - 30-60% MVI
  - >5 cm - 60-90% MVI

- large tumors (>5 cm) often require major hepatectomy

Ng et al. Ann Surg Oncol 2005
Llovet et al Semin Liv Dis 2005
HCC resection: tumor size >5 cm

- role of portal vein embolization (PVE) if future liver remnant is <40-50%
  - morbidity and mortality rate of 2.2% and 0%
  - impaired regeneration in cirrhotic liver (9% vs 16%)
- mortality after major resection up to 10%
- 5-year survival 30-35%
- risk factors for impaired long-term survival:
  - macroscopic vascular invasion
  - multiple lesions
  - underlying cirrhosis

Early HCC (<2 cm): resection or ablation?

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Are ablation and resection comparable for treatment of early hepatocellular carcinoma?</th>
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<tr>
<th></th>
<th>Radiofrequency ablation</th>
<th>Liver resection</th>
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<tbody>
<tr>
<td>No of patients</td>
<td>218 (5 centers)</td>
<td>132 (2 centers)</td>
</tr>
<tr>
<td>Perioperative mortality</td>
<td>0%</td>
<td>0.8%</td>
</tr>
<tr>
<td>Sustained complete response</td>
<td>97.2%</td>
<td>100%</td>
</tr>
<tr>
<td>5-year overall survival rate</td>
<td>55%</td>
<td>70%</td>
</tr>
<tr>
<td>5-year recurrence rate</td>
<td>80%</td>
<td>68%</td>
</tr>
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</table>

Arii S et al. Hepatology 2000  
Roayaie et al. Hepatology 2013  
Majno et al. Hepatology 2010  
Mazzaferro et al. Semin Liver Dis 2014
Resection versus ablation for HCC

HCC resection: number of tumors

- multiple HCCs has been traditionally considered as contraindication for surgical resection due to the high recurrence rate (5-year disease-free survival of 10%) and lower 5-year survival
- however in selected cases surgical resection can offer better survival than TACE – in some series up to 39-58% (especially if tumors are within Milan criteria in patients not suitable for liver transplantation)

Ng et al. Ann Surg Oncol 2005
Ishizawa T Gastroenterology 2008
Yin et al. J Hepatol 2014
HCC resection
- Anatomic vs Non-anatomic

- HCC spreads and metastasizes via portal venous system
- Anatomical resections can reduce local recurrence without the increased operative risk, especially in tumors between 2 and 5 cm

Eguchi et al. Surgery 2008
Yin et al. J Hepatol 2014
Mazzaferro et al. Semin Liver Dis 2014
Shidoh et al. J Hepatol 2016
HCC resection
- Anatomic vs Non-anatomic

Shidoh et al. J Hepatol 2016
HCC resection: margin

Some studies showed that resection margin of 2 cm provides better survival outcome than margin <1 cm. However, in the meta-analysis, no differences in overall survival and recurrence rate between resection margin <1 cm and ≥1 cm were observed. Shi et al. Ann Surg Oncol 2007, Tang et al. Hepatogastroenterology 2012, Lee et al. World J Surg 2016.
HCC resection: portal hypertension

Differences in assessment of portal hypertension:

- direct measurements (transjugular HVPG – PH if HVPG > 10 mm Hg)
- non invasive:
  - CT-based liver/spleen volume ratio
  - surrogate markers of portal hypertension (esophageal varices, splenomegaly and platelets count below 100 000/mm$^3$)

Bruix et al. Gastroenterology 1996
Cucchetti et al Ann Surg Oncol 2009
HCC resection: portal hypertension

- major resections (>3 segments) in patients with portal hypertension are associated with 50% mortality
- minor resections should be cautiously evaluated (high complications rate – postoperative liver failure)

Boleslawski et al. BJS 2012
Iranmanesh et. Al J Hepatol 2014
Management of HCC with portal vein thrombosis

Mazzaferro et al. Semin Liver Dis 2014
HCC resection: vascular invasion

- Invasion of portal trunk, hepatic veins or vena cava is associated with poor outcome.

- In selected patients (normal liver function + excellent general status) resections combined with tumor thrombus removal can provide favorable results.

Inoue et al. Surgery 2009
Shi et al. Ann Surg Oncol 2010
Kokudo et al. J Hepatol 2014
HCC resection and tumor rupture

- Spontaneous rupture of HCC ranges between 5% and 15%.
- Transarterial embolization is a first line treatment to achieve hemostasis.
- Liver resection is an option if negative surgical margin can be achieved.

Management of ruptured hepatocellular carcinoma in a European tertiary care center

Lymph node dissection for HCC

➢ Lymph node dissection during liver resection for HCC remains controversial

➢ In the recent systematic review:
  - prevalence of lymph node dissection was 52%
  - incidence of lymph node metastasis (LNM) was 44.5%
  - 3- and 5-year survival in patients with LNM was 27.5% and 20.8% compared to 60.2% and 42.6% in patients without LNM

*Amini et al. J Gastrointest Surg 2014*
HCC resection: extrahepatic disease

- diaphragmatic involvement
  - infrequent
  - recommended en-bloc resection

- adrenal gland metastasis – adrenalectomy can be recommended in patient without or with well-controlled intrahepatic disease

- peritoneal metastases – in very selected patients, scarce data

Yamashita et al. Surg Today 2011
Chua et al. Surgical Oncology 2012
Technical consideration in liver resection for HCC

- Laparoscopic liver resection
- Portal clamping (Pringle)
- Anterior approach
- Parenchyma transection
- ALPPS
Laparoscopic vs open liver resection for HCC

- Systematic review of 10 studies reported on 494 patients – 213 laparoscopic liver resection and 281 open liver resection for HCC.
  - lesser blood loss and blood transfusion requirements
  - lesser overall morbidity including decompensation of liver cirrhosis
  - shorter length of stay
  - no differences in oncological outcomes (margin and survival)

French multicenter study on 351 patients showed similar results;

However:

- 90% minor resections
- data from 1998-2010
- no randomized studies

Soubrane et al. HPB 2013
Portal clamping during resection of HCC

- Intermittent or continuous?
- In the systematic review and meta-analysis no advantage of the standard use of portal clamping

  *Rahbari et al. BJS 2008*

- However, in two recent studies portal clamping was associated with:
  - lower overall patient survival
  - early recurrence

  Wang et al. Ann Surg Oncol 2009*
Parenchyma transection in cirrhotic liver

- In the Cochrane review there were no differences between the techniques, however Kellyclasie was the quickest and most cost-efficient

  Garusamy et al. Cochrane Database Syst Rev 2009

- Depends on the preference, skills and experience of the operating surgeon
Anterior approach in HCC

- Proposed by group from Hong Kong in case of large HCC in the right hemiliver

Anterior approach in HCC

The same group showed in the randomized controlled trial that anterior approach in HCC >5 cm was associated with:

- lower transfusion requirements
- lower number of patients requiring transfusions
- better overall survival (but not disease free survival)

The use of ALPPS in HCC

- A single center study from Hong Kong showed promising results based on their experience in 17 patients.
  - Inclusion criteria: Child A liver cirrhosis, ICG R15 <20% at 20 minutes, FLR/ESLV <40%, platelets >100,000/mm^3
  - Volume increment after 6 days was 49% with no postoperative mortality.

- Data from ALPPS registry (35 patients with HCC) showed rapid hypertrophy 47% (76% CLRM) with fivefold higher 90-days mortality of 31% (7% CLRM).

- Age >61 years was the risk factor for mortality.

Outcome after surgical resections for HCC

- 5-year survival of 60-80%
- peri-operative mortality of 2-3%
  - drop from 15% in 1980’ (!)
- blood transfusion requirement less than 10%
  - drop from 80-90% in the last two decades (!)

Makuuchi et al. Liver Transpl 2004
Llovet JM, Bruix J. J Hepatolo 2008
Outcome after surgical resections for HCC

- up to 70-80% recurrence within 5 years (both intrahepatic metastases and de novo tumors)

Risk factors for overall survival and for recurrence after resection

**Overall survival**
- Macrovascular invasion
- Tumor size >5 cm
- Preoperative bilirubin elevation
- Esophageal varices
- Cirrhosis

**Recurrence**
- Microvascular invasion
- Poor histological differentiation
- Satellites
- Multifocal disease

*Torzilli et al. Ann Surg 2013*
Resection vs transplantation for HCC


(A) <3 cm

(B) >3 cm

Diagrams showing survival rates and Log Rank p-values for resection vs transplantation for HCC.
Resection vs liver transplantation for HCC

- limited organ availability
- lifelong immunosuppression after liver transplantation

- liver resection for early HCC as first line treatment with curative intention and **salvage liver transplantation** in cases of HCC recurrence → better selection of patients for liver transplantation

*Majno et al. Hepatology 2000*
*Poon et al. Ann Surg 2002*
Resection vs liver transplantation for HCC

- risk factors: presence of cirrhosis, diameter >3 cm, microscopic vascular invasion, satellite nodules and poor differentiation

Fuks et al. Hepatology 2012
Ferrer-Fabrega et al. Hepatology 2016
Conclusions

- Resection is a first-line treatment option for HCC in patients with solitary tumor and very well preserved liver function (Child-Pugh A)
- Multidisciplinary approach is necessary in patients with HCC in cirrhotic liver
- 5-year survival of 60-80% can be achieved after liver resection with peri-operative mortality of 2-3%
- Recurrence rate after liver resection is as high as 70% at 5 year
SAVE THE DATE 21-23 OCTOBER 2016
in Rotterdam
Thank you for your attention

Questions?