Hepatocellular Cancer

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Outline

- definition of HCC
- epidemiology of HCC
  - determinants
  - distribution/incidence
- AASLD diagnostic algorithm for HCC
- multidisciplinary treatment of HCC
  - considerations
  - modalities
  - treatment algorithm

Hepatocellular Cancer (HCC)

a.k.a. Hepatoma, Hepatocellular Carcinoma

- definition:
  - a primary malignancy **of** the liver (as opposed to metastases from a extra-hepatic primary cancer, e.g. lung, colon, breast)
  - normal liver constituents → malignant progeny:
    - hepatocytes (liver cells) → hepatocellular cancer
      - commonest, **80 – 90%** of primary liver malignancy
    - cholangiocytes (bile duct cells) → cholangiocarcinoma
      - not very common, ≈ 10%
    - vascular/connective tissue → various sarcomas
      - rare

Epidemiology of HCC

Determinants

- aetiology:
  - **chronic hepatocyte inflammation**
    - viral hepatitis - #1 & #2
      - chronic HBV infection – developing world
        - vertical transmission during birth/infancy, 90% chronic infection (≤ 5% in immunocompetent adult)
        - DNA virus, so also has oncogenic potential*
      - chronic HCV infection – developed world
        - pre 1989 blood transfusion, "high risk" behaviours
        - chronic infection 50-90%, 10-30% cirrhosis at 20 years
    - alcohol-related chronic liver disease - #3
    - other chronic liver diseases: NAFLD, cholestatic, hemochromatosis, etc

Epidemiology of HCC

Incidence Worldwide

- incidence:
  - worldwide ≈ **0.7 – 1.0** million new cases/year (≈ 16/100,000 person/years)
  - 6th commonest malignancy
  - incidence varies by prevalence of risk factors
    - 10-20/100,000 – South-East Asia, sub-Saharan Africa
      - **accounts for 80% of world burden of disease**
      - **70% HBV**, 20% HCV, 10% etoh
    - 1-3/100,000 – Europe, North America*
      - **50-70% HCV**, 10-20% HBV, 20% etoh, 10% other
  - 3rd leading cause of malignancy-related death

Epidemiology of HCC

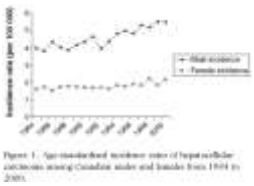
Incidence Worldwide

- incidence varies depending on prevalence of risk factors in specific population
- also note ≈ 90% of risk is avoidable, preventable or treatable…..

Epidemiology of HCC

Incidence in Canada

- **increasing** in Canada
  - ≈ 40% relative increase from 1984 to 2000
    - 2000 incidence
      - ♂ 5.5/100,000
      - ♀ 2.2/100,000
  - 2013 incidence
    - ♂ 6.9/100,000
    - ♀ 1.9/100,000
  - predicted up to 15/100,000
- primarily related to rising prevalence HCV, NAFLD



Epidemiology of HCC

HCC & ESLD

- End-Stage Liver Disease (ESLD), a.k.a. cirrhosis
  - common end point of chronic liver diseases
  - principle risk factor for HCC
    - underlies 80-90% of cases
  - HCC is now leading cause of death in patients with ESLD
    - management of other complications has improved
  - **implications on management**:
    - hepatic functional reserve defines/constrains treatment options
    - unstable pro-neoplastic parenchymal field defect influences treatment success
  - identifiable at-risk group → **surveillance**

CTP Classification of ESLD

Child-Turcotte (1964), Pugh modification (1973)

	1	2	3
albumin (g/L)	>35	28 – 35	<28
bilirubin(μmol/L)	<35	35 – 50	>50
INR	<1.7	1.7 – 2.3	<2.3
ascites	none	controlled	refractory
encephalopathy	0	I – II	III – IV

- A = 5 to 6 points "compensated"
- B = 7 to 9 points
- C = 10 to 15 points

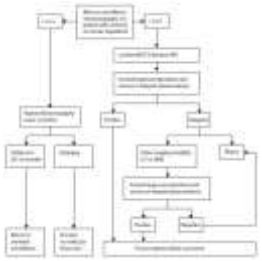
} "decompensated"

Diagnosis of HCC

- two scenarios:
  - high-risk individual* in surveillance programme
    - AASLD guidelines 2011
      - q6monthly US
      - serum AFP no longer recommended
  - symptomatic or incidental liver mass
    - history, physical, laboratory, imaging evidence of ESLD?
      - YES → AASLD 2011 diagnostic algorithm
      - NO → hx & px, laboratory investigations (including appropriate tumour markers), **high-quality contrast enhanced dynamic imaging with expert interpretation**, NO biopsy without HPB Surgical consultation

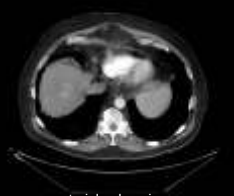
Diagnosis of HCC

AASLD Practice Guidelines 2011

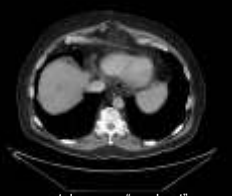


Imaging-Based Diagnosis of HCC

CT

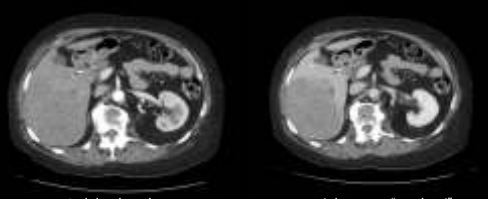


arterial enhancing



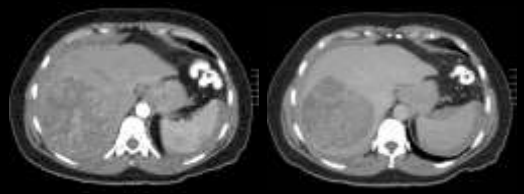
portal venous "washout"

Imaging-Based Diagnosis of HCC
CT



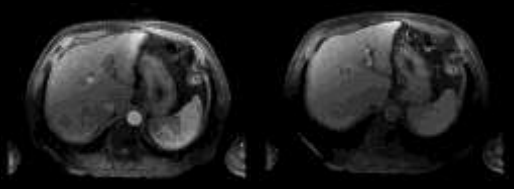
arterial enhancing | portal venous "washout"

Imaging-Based Diagnosis of HCC
CT



arterial enhancing | portal venous "washout"

Imaging-Based Diagnosis of HCC
MRI



arterial enhancing | portal venous "washout"

Treatment of HCC

- in North America and Europe at time of presentation:
  - ≈ 1/3rd of patients have potentially curable, localized disease
  - ≈ 2/3rd of patients have extensive hepatic or metastatic disease which precludes chance of cure
- options defined by:
  - tumour factors – stage and location
  - liver factors – functional hepatic reserve
  - medical comorbidities & performance status

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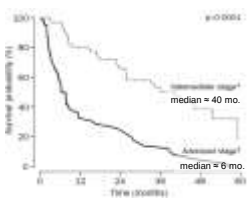
Treatment of HCC

- natural history
  - untreated survival:
    - 1-year ≈ 50%
    - 3-year ≈ 25%
  - influenced by:
    - stage of malignancy
    - severity of ESLD



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Treatment of HCC
Considerations

- factors to be considered in treatment planning:
  - stage/extent of malignancy
    - localized – size and number of lesions
    - locally advanced – multinodular (4+), vascular invasion
    - metastatic – perihepatic lymph node or systemic (lung, bone)
  - technical factors
    - location and proximity to intra or extrahepatic structures
  - presence and severity of underlying ESLD
    - Child-Turcotte-Pugh classification status
    - absence or presence of "important" portal hypertension, i.e. P-S gradient >10
  - patient health and performance status
    - non-hepatic medical comorbidities

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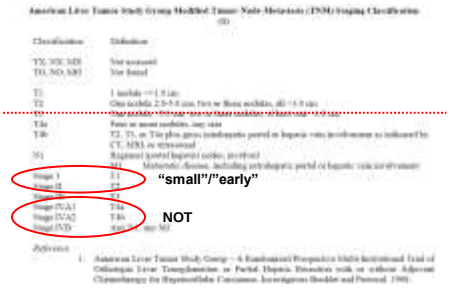
HCC Staging Classifications

ALTSG staging (employed by UNOS)



“small”/“early”

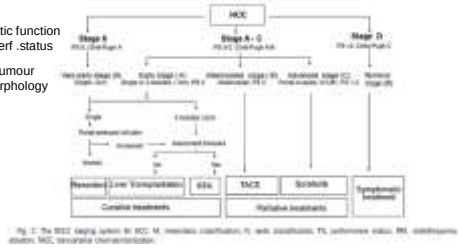
NOT

HCC Staging Classifications

Barcelona Clinic Liver Cancer staging

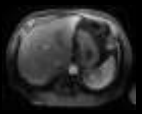
hepatic function & perf .status

tumour morphology

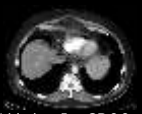


HCC Staging Examples

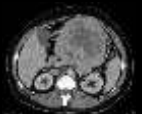
ALTSG & BCLC systems



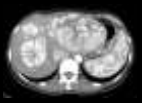
stage I (single, < 2cm)
“very early”



stage II (single, < 5cm OR 2-3, < 3 cm)
“early”



stage III (single, > 5cm OR 2-3 > 3 cm)
“early”



stage IV (4+ OR vascular invasion OR mets)
“intermediate to advanced”

Treatment of HCC - Options

- multiple treatment options:
  - resection
  - ablative techniques
  - transplantation

  } curative intent

  - transarterial techniques
  - external beam radiotherapy
  - systemic therapy
  - best supportive care

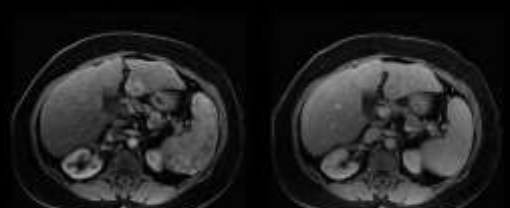
  } palliative intent

Treatment of HCC - LR

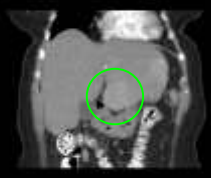
- resection:
  - indications:
    - solitary nodule, no size constraint
    - no extra-hepatic disease
    - adequate remnant (≥ 50%)
    - no portal hypertension (therefore CTP “A+”)
    - healthy enough to tolerate major surgical procedure
  - pros:
    - not constrained by allograft availability
  - cons:
    - applicability (< 5% of patients in North America/Europe)
    - intra-hepatic recurrence (60-70% at 5 years)
    - may precipitate decompensation (perioperative mortality up to 10%)

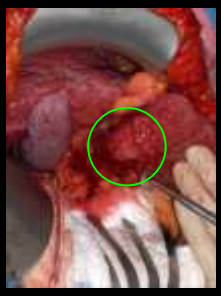
segment III HCC

(background cirrhosis 2° NAFLD)



segment III HCC
(background cirrhosis 2° NAFLD)





segment III HCC
(background cirrhosis 2° NAFLD)

Treatment of HCC - Ablation

- ablative techniques – thermal or chemical
  - indications:
    - solitary nodule, diameter < 5 cm for thermal, < 3 cm for chemical
    - no extrahepatic disease
    - minimal to moderate ESLD (i.e. CTP "A" or "B")*
  - pros:
    - for "small" HCC compared to resection: ≈ survival, ↓ morbidity
  - cons:
    - size constraint
    - treatment site recurrence (> resection)
    - intrahepatic recurrence (= resection)

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Treatment of HCC - LT

- transplantation:
  - indications:
    - "early" HCC (**Milan criteria**, UCSF criteria)
    - no extrahepatic disease
    - healthy enough to tolerate major surgical procedure
    - no contraindications to life-long immunosuppression
  - pros:
    - ultimate R0 resection
    - eliminates at-risk parenchyma
    - addresses underlying ESLD
  - cons:
    - allograft availability

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Liver Transplantation for HCC
The Milan Criteria

- Mazzaferro V et al (Milan). N Engl J Med 1996.
  - prospective cohort study (n = 48) , single institution experience with liver transplantation for *unresectable* HCC meeting criteria:
    - **single tumor ≤ 5cm**
    - **3 or less tumors, none > 3cm in size**
    - **no (macroscopic) vascular invasion**
    - **no perihepatic lymphadenopathy**

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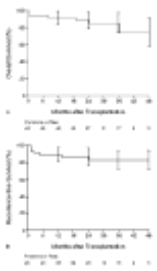
Liver Transplantation for HCC
The Milan Criteria – Mazzaferro et al.

- survival outcomes:
  - median follow-up 26 months
  - **74%** 4-year OS
  - **83%** 4-year DFS



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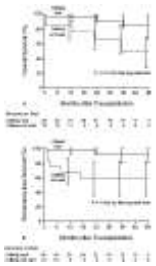
Liver Transplantation for HCC

The Milan Criteria – Mazzaferro et al.

- survival outcomes – by final pathology:
  - 35/48 patients (73%) met criteria
    - 85% 4-year OS
    - 92% 4-years DFS
  - 13/48 patients (27%) exceeded criteria
    - 50% 4-year OS
    - 59% 4-year DFS



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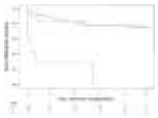
Liver Transplantation for HCC

Beyond the Milan Criteria – UCSF

- Yao F et al. Hepatology 2001.
  - case series of 70 liver transplant recipients with HCC, 1988 – 2000
    - 5-year survival by pathological stage:
      - 72% T1/T2 (Milan criteria)
      - 74% T3 (1 nodule > 5 cm, 2-3 nodules one > 3 cm)
      - 0% T4 (4 or more nodules of any size)

} ALTSG staging



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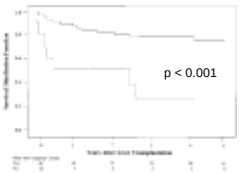
Liver Transplantation for HCC

The UCSF Criteria – Yao et al.

- UCSF Criteria:
  - **single tumor ≤ 6.5 cm**
  - **≤ 3 tumors, largest ≤ 4.5 cm, total diameter ≤ 8 cm**



5-year survival 75%

5-year survival < 30%

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LT for HCC in Atlantic Canada

- MOTP Halifax, Dec 1 2004 to Nov 30 2009
  - 127 candidates received 1st liver transplant
    - indication:
      - decompensated ESLD 75.6% (96)
      - **malignancy 18.1% (23)**
      - ALF 3.1% (4)
      - other 3.1% (4)
    - top 5 liver disease indications:
      - **HCC 18.1% (23)**
      - HCV-related ESLD 16.5% (21)
      - PSC 15.0% (19)
      - PBC 12.6% (16)
      - etoh-related ESLD 11.0% (14)

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LT for HCC in Atlantic Canada

- no survival difference by ESLD vs. HCC indication

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Treatment of HCC - TACE

- transarterial techniques – TAE, TACE and TARE
  - indications:
    - solitary or multinodular disease
    - no extrahepatic disease*
    - minimal to moderate ESLD (i.e. CTP "A" or "B")*
    - patent portal vein with hepatopetal flow*
  - pros:
    - wide applicability
    - prolongs survival, compared to best supportive care
  - cons:
    - not curative
    - may precipitate decompensation

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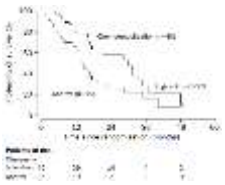
TACE

landmark RCTs

- Llovet JM et al. 2002.
  - RCT TACE vs. BSC
  - mean survival (months)
    - TACE 29 vs. 18 BSC
  - 3-year overall survival
    - TACE 30% vs. 17% BSC



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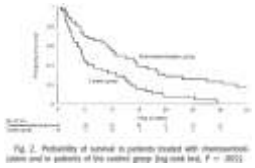
TACE

landmark RCTs

- Lo CM et al. 2002.
  - RCT TACE vs. BSC
  - 3-year overall survival
    - TACE 26% vs. 3% BSC
  - HR = 0.49 (95%CI: 0.29-0.81, p = 0.006)



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Treatment of HCC - EBRT

- external beam radiotherapy:
  - emerging therapy
  - indications:
    - solitary nodule, no size constraint
    - no extra-hepatic disease*
    - adequate remnant (≥ 50%)
    - minimal to moderate ESLD (i.e. CTP “A” or “B”)
  - pros:
    - option for patients who are ineligible for established therapies
  - cons:
    - non-curative
    - role/effectiveness still being established

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Treatment of HCC - Systemic

- systemic therapy – sorafenib
  - oral multikinase inhibitor of VEGF-R, PDGF-R, Raf
  - indications:
    - advanced disease
    - minimal ESLD (i.e. CTP “A”)
  - pros:
    - prolongs survival*, compared to best supportive care
  - cons:
    - not curative
    - applicability – CTP “A”
    - prolongs survival?

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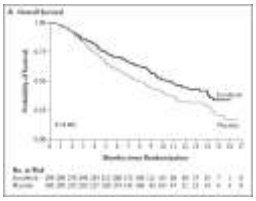
Sorafenib - SHARP

- improves survival:
  - median survival:
    - 10.7 vs. 7.9 months
      - RD = 2.8 months
      - RR = 1.35
  - 1-year OS:
    - 44% vs. 33%
      - RD = 11%
      - RR = 1.33



HR = 0.69; 95%CI, 0.55-0.87; p < 0.001

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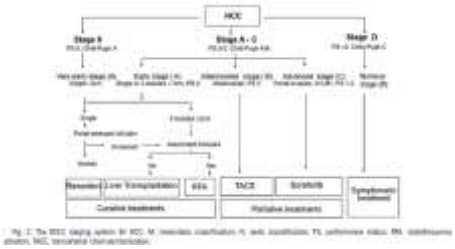
Treatment of HCC - Summary

Barcelona Clinic Liver Cancer algorithm



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Hepatocellular Cancer - Summary

- expect incidence to increase
- in long-run, 90% of causality is preventable
- evidence-based surveillance recommendations for at-risk individuals exist
- currently, majority of patients are incurable at diagnosis
- treatment constrained by associated ESLD
- for “early” HCC, liver replacement is optimum curative-intent management
- even when not curable, thoughtful multimodality management (of malignancy and liver disease) can provide meaningful survival to patients

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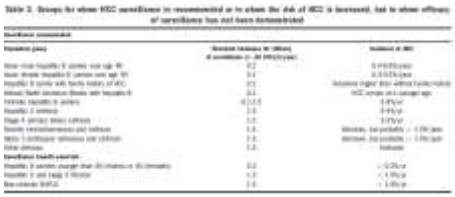
Extra Slides

HCC Risk Groups*



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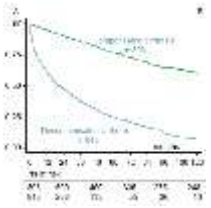
ESLD – Natural History

- survival:
  - median:
    - compensated > 12 yrs
    - decompensated ≈ 2 yrs
  - 5-year:
    - compensated ≈ 80%
    - decompensated ≈ 25%



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segment III HCC

(background cirrhosis 2° NAFLD)