This guideline is a statement of consensus of the GI Disease Site Team regarding their views of currently accepted approaches to treatment. It is not intended to replace the independent medical judgement of the physician in the context of individual clinical circumstances to determine any patient’s care or treatment.
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Hepatocellular Carcinoma
GI Practice Guideline

Background

- Most common in subsahara Africa, Orient.
- Risk factors:
  - Infection
    - Hep B, C esp. genotype 1b
  - Cirrhosis
  - Environmental
    - Androgenss - aflatoxins - EtOH
    - tobacco - N-nitrosylated compounds - algae toxins
    - Thorotrust contrast medium - pyrrolizidine alkaloids - ?betel nuts?
- Presentation
  - abdominal pain - anorexia - bone pain
  - intraperitoneal bleed - paraneoplastic hypoglycemia/erythrocytosis
  - hypercalcemia - diarrhea.
### TNM Staging

<table>
<thead>
<tr>
<th>Primary Tumor (T)</th>
<th>Stage grouping</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td>Stage I T1 N0 M0</td>
</tr>
<tr>
<td>T1</td>
<td>Stage II T2 N0 M0</td>
</tr>
<tr>
<td>T2</td>
<td>Stage IIIA T3 N0 M0</td>
</tr>
<tr>
<td>T3</td>
<td>Stage IIIB T4 N0 M0</td>
</tr>
<tr>
<td>T4</td>
<td>Stage IIIC Any T N1 M0</td>
</tr>
<tr>
<td></td>
<td>Stage IV Any T Any N M1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Regional lymph nodes (N)</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>NX</td>
<td>Positive</td>
</tr>
<tr>
<td>N0</td>
<td>No regional lymph node metastasis</td>
</tr>
<tr>
<td>N1</td>
<td>Regional lymph node metastasis</td>
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</table>

<table>
<thead>
<tr>
<th>Distant metastasis (M)</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>MX</td>
<td>Positive</td>
</tr>
<tr>
<td>M0</td>
<td>No distant metastasis</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastasis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Fibrosis Score (F)</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>F0</td>
<td>Positive</td>
</tr>
<tr>
<td>F1</td>
<td>Severe fibrosis or cirrhosis</td>
</tr>
</tbody>
</table>

### Okuda Staging System for Hepatocellular Carcinoma

The okuda system is commonly used for staging hepatocellular carcinoma. Survival correlates with the Okuda stage in untreated patients (8.3, 2.0 and 0.7 for stages I, II, and III, respectively). Adapted from Okuda, K. Ohtuiki, T, Obata, H, et al., Cancer 1985; 56:918
Overall Pathway – Hepatocellular Carcinoma

Presentation

Required Work-up

Surgical Assessment

LRCP Referral
MO + RO

Potentially Curative Rx  Palliative Rx
Investigations – Required Work-up

- **CNCCN guidelines**
  - H&P
  - alkaline phosphatase
  - BUN
  - Hepatitis B surface antigen
  - Hepatitis C antibodies
  - Hepatitis panel
  - LDH, PT or INR
  - creatinine
  - CT/MRI
  - albumin
  - transaminases
  - albumin
  - protein
  - CBC
  - platelets
  - Bilirubin
  - PT or INR
  - Chest x-ray
  - AFP

- Biopsy if AFP < 400 ng/ml (HepB SAg-) / < 4000 ng/ml (HepB SAg+)

- **American Association for the Study of Liver Diseases (AASLD)**
  - See next page.
  - More emphasis on imaging characteristics and size (>1 cm)
  - AFP cutoff for biopsy <200 ng/ml

**Biopsy risks controversial**
- Seeding of needle tract reported in 0 – 5% of patients in series.
AASLD (2005) Diagnostic Approach

Fig. 1 A suggested algorithm for investigation of a nodule found on ultrasound during screening or surveillance. Note that nodules smaller than 1 cm initially which enlarge over time should be investigated using one of the other two algorithms shown depending on the size of the nodule. The typical vascular pattern referred to means that the lesion is hypervascular in the arterial phase, and washes out in the portal/venous phase. All other patterns are considered atypical.
Investigations – Surgical Assessment

- Needed in regards to resectability (tumor and patient characteristics)
- Will be to some extent determined by individual surgeon
- For example: Barcelona Clinic Liver Cancer approach/AASLD guideline) – see next page

<table>
<thead>
<tr>
<th>Chemical and Biochemical Parameters</th>
<th>Scores (Points) for Increasing Abnormality</th>
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<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Encephalopathy (grade)</td>
<td>None</td>
</tr>
<tr>
<td>Ascites</td>
<td>None</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>&gt; 3.5</td>
</tr>
<tr>
<td>Prothrombin time prolonged (sec)</td>
<td>1 – 4</td>
</tr>
<tr>
<td>Bilirubin (mg/dL)</td>
<td>1 – 2</td>
</tr>
<tr>
<td>– For primary biliary cirrhosis</td>
<td>1 – 4</td>
</tr>
</tbody>
</table>

**Original**

Class A: 5 – 6 points; Class B = 7 – 9 points; Class C= 10 – 15 points.

**Alternative:**

Class A: Good operative risk
Class B: Moderate operative risk
Class C: Poor operative risk
Barcelona / AASLD Approach to Surgical Assessment

HCC

Very early stage
- Single < 2cm

Early stage
- Single or 3 nodules < 3cm, PS 0

Intermediate stage
- Multinodular, PS 0

Advanced stage
- Portal invasion, N1, M1, PS 1-2

Terminal stage
- Portal invasion, N1, M1

PST 0, Child-Pugh A

PST 0-2, Child-Pugh A-B

PST >2, Child-Pugh C

Portal pressure/ bilirubin

Increased
- Associated diseases

Normal
- No

Yes

Resection

Liver Transplantation (CLT / LDLT)

PEI/R F

Chemoembolization

New Agents

Curative Treatments

Randomized controlled trials

Symptomatic

Fig. 2 Strategy for staging and treatment assignment in patients diagnosed with HCC according to the BCLC proposal
Prognosis in US. Population by Surgical/Interventional Treatment Received

“Curative”

“Palliative”

N.B. Not always deemed appropriate for stage, by external review.

*J. Hepat* 1/2006, p. 158
Treatment – Curative Intent

- Treatment in addition to surgery – curative intent
  - Neoadjuvant
    - 131-I – Lipiodol intra-arterial treatment
    - case series 19/34 pts objective response
  - Intra-arterial chemotherapy
    - conflicting series. Most show reduction in size but no large survival difference
    - One controlled trial of resectable tumours demonstrated worse survival in Rx group, presumably because of delay to surgery (Br J Surg 1995 Jan;82(1):122-6)
    - Not recommended by AASLD guidelines
    - Should be reserved for tumours of borderline resectability only
  - Adjuvant
    - Adjuvant therapy: most positive study is Lau et al (Lancet 1999) with I-131 Lipiodol 85 vs 46% 3YS. Current (Oct 2006) Phase III trial at NCI ongoing and open to accrual (NCT00027768)
Treatment – Palliative-intent therapy (localized)

- Radiofrequency ablation / Percutaneous ethanol ablation
  - neither of these has directly been compared to BSC alone, however, survivals and local control rates are generally better than what would be expected; > 75-80% at 2 years. Some consider this “curative”. Studies limited by short f/u (2-5 years)
    - External beam radiation research protocol
    - Transarterial embolisation with $^{131}$Iodine lipiodol
      - One randomized trial with benefit in pts with portal vein thrombosis.
        - 6 month survival 48% vs 0% (27 pts total), 9 month survival 7% vs 0%. (Nucl Med 1994 Nov;35(11):1782-7)
    - Transarterial chemotherapy/embolisation (‘HACE’ or ‘TACE’)
      - Benefit very dependent on patient selection. Recommended by AASLD
        - A prognostic index of the survival of patients with unresectable hepatocellular carcinoma after transcatheter arterial chemoembolization, Cancer 2000 Jan 1;88(1):50-7
    - Transarterial chemotherapy/embolisation + lipiodol (‘HALCE’)
      - Two randomized trials with survival benefit e.g. Hepatology 2002 May;35(5):1164-71, HR 0.49.
    - Transarterial chemotherapy/embolisation + $^{131}$I- lipiodol
      - Unique to LRCP?
Treatment – Palliative-intent therapy (systemic)

- Tamoxifen – negative RCTs
- Octreotide – negative RCTs however follow-up too short. Ongoing HECTOR trial in Europe pending final analysis
- Chemotherapy
  - Doxorubicin vs. BSC 10.6 vs 7.5 weeks OS (Lai et al, Cancer 1988;62(3):479-83)
  - Resp rate around 20%, higher than 5FU or etoposide, but no OS difference
  - Gemcitabine, Capecitabine [11% RR] also in series only
  - Combination therapy: cisplatin/5FU, cisplatin/doxorubicin, gemcitabine/cisplatin etc. RR around 10-45% in series
    - ECF: 15% RR in 21 pts (1/21 pCR)
  - Little if any QOL data
  - Adding interferon – inc RR? but not survival
- Trials – preferable – over 50 active trials at clinicaltrials.gov as of Oct 2006
Overall pathway – Hepatocellular Carcinoma (summary)

Presentation
Liver mass suspicious for hepatocellular carcinoma (HCC) or histologically confirmed HCC

Required Work-up
- H&P
- Hepatitis panel
- Hepatitis B surface antigen
- Hepatitis C antibodies
- Bilirubin, transaminases, alkaline phosphatase, LDH
- PT or INR, albumin, protein, BUN, creatinine
- CBC, platelets
- AFP
- CT/MRI
- Chest x-ray

Surgical Assessment
- Assess liver status Child-Pugh A/B vs C
- Biopsy?
- Partial hepatectomy feasible?
  - solitary HCC in liver, no inv of hepatic artery, no severe portal HTN, etc.
- Transplant candidate?
  - unresectable HCC <5cm, or up to 3 lesions < 3 cm, no gross vascular inv, no nodal metastases, etc.
- Borderline resectability?

Potentially Curative Rx
- Partial hepatectomy
- Transplant
- Assessment at LRCP regarding
  - Neoadjuvant embolisation with \(^{131}\text{I-lipiodol}\)
  - Adjuvant embolisation with \(^{131}\text{I-lipiodol}\)

Palliative Rx
- Localized therapy
  - External beam radiation (experimental protocol/Dr. M. Lock - concurrent 5FU)
- Radiofrequency ablation/ Percutaneous ethanol ablation
- Transarterial embolisation with \(^{131}\text{I-lipiodol}/ \text{cisplatin} / \text{doxorubicin}\)
- Systemic therapy:
  - Clinical trial or best supportive care
  - Selected patients: consider chemotherapy (doxorubicin or ECF [ECF = Epirubicin 60 mg/m\(^2\) + Cisplatin 50 mg/m\(^2\) q21d; 5FU daily 200mg/m\(^2\) infusion] or PIAF [PIAF = Cisplatin 20mg/m\(^2\) day 1-4, doxorubicin 40mg/m\(^2\) day 5, 5FU 400mg/m\(^2\) day 1-4, \(\alpha\)-IFN 5MU/m\(^2\) SC days 1-4, all q21 days}); survival advantage not clearly demonstrated.
- Consider long-acting octreotide
References


1. AFP (a – fetoprotein) sensitivity 41-65%, spec 80-94%; +’ve likelihood ratio 3.1-6.8; -’ve LR 0.4-0.6 using cutoffs of 16-100 µg/L

2. Partial hepatectomy: 5YS 30-90%. Requires Child-Pugh A or B with good PS. Consider preoperative portal vein embolization to induce hypertrophy.


5. 50-60% RR. Need KPS>60-70, no severe weight loss. HALCE contraindications: PV thrombus, encephalopathy, biliary manipulation Hx/obstr; relative: bili>35, AST>100, >50% of liver replaced by tumour, CHF/CRF, ascites, variceal bleed, low plt’s. I-131 lipiodol/chemoembolisation at LRCP; other centres use only one modality/no radiolabelled oil – evidence controversial for that (e.g. lipiodol alone insuff.: N Engl J Med 1995;332:1256-61.)

6. Evidence controversial. Hepatology 2002(3):687 negative but OS only 2 mos each arm and 60% no Rx or only 1 dose. HECTOR study ongoing. Kuroumalis et al. 1998; Gut 62 : positive but retrospective.
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