Manchester Cancer

Central Manchester University Hospitals NHS
NHS Foundation Trust

# Greater Manchester and Cheshire HPB Unit Guidelines for the Assessment & Management of Hepatobiliary and Pancreatic Disease

# Chapter 6

# Contents

# 6. Hepatocellular carcinoma

## 6.1. *Introduction:*

This guidance regarding hepatocellular carcinoma [HCC] is based on the:

- American Association for the Study of Liver Disease (AASLD) Guidance on the Management of HCC (2010)
- British Society of Gastroenterology guidance (2003)
- The BCLC (Barcelona Clinic Liver Cancer) algorithm for management of HCC
- The European Association for the Study of Liver Disease (EASL) and European Organisation for Research and Treatment of Cancer (EORTC) Clinical Practice Guidelines (2012)
- Liver Advisory Group on behalf of NHSBT - Liver Transplantation: Selection Criteria and Recipient Registration (March 2014)

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## 6.2. *HCC surveillance*

### Categories of adult patients in whom surveillance is recommended:

1. The following patients at high risk for developing HCC should be entered into surveillance programs:
    1. Cirrhotic patients, Child-Pugh stage A and B
    2. Cirrhotic patients, Child-Pugh stage C awaiting liver transplantation
    3. Non-cirrhotic HBV carriers with active hepatitis or family history of HCC
    4. Non-cirrhotic patients with chronic hepatitis C and advanced liver fibrosis F3
2. Surveillance should be performed by experienced personnel in all at-risk populations using abdominal ultrasound every 6 months.

    Exceptions: A shorter follow-up interval (every 3-4 months) is recommended in the following cases:
    1. Where a nodule of less than 1 cm has been detected
    2. In the follow-up strategy after resection or locoregional therapies
3. Accurate tumour biomarkers for early detection need to be developed. Data available with tested biomarkers (i.e. AFP, AFP-L3 and DCP) show that these tests are suboptimal for routine clinical practice
4. Patients on the waiting list for liver transplantation should be screened for HCC in order to detect and manage tumour progression and to help define priority policies for transplantation

### Recall policy

See: *Surveillance recall policy and diagnostic algorithm* (Figure 1)

## 6.3. *Screening for underlying liver disease:*

1. HCC is much more common in patients with underlying liver cirrhosis (especially due to viral hepatitis and haemochromatosis) and in patients with chronic hepatitis B without cirrhosis. The majority (about 90%) of patients with HCC will have pre-existing diagnosed liver disease.
2. Where liver disease is not diagnosed prior to the development of HCC, all patients should be screened for:
    - Alcohol abuse
    - Non-alcoholic fatty liver disease (NAFLD)
    - Chronic hepatitis B and hepatitis C
    - Iron overload (haemochromatosis)
    - Autoimmune liver disease
3. In patients with an expected short prognosis (< 2 months) genetic tests for haemochromatosis and hepatitis B serology should be done at the first assessment. This screening is necessary as (genetic) family and household contacts may also be at risk of these conditions and need screening themselves. Screening is needed even for patients who apparently have another cause of liver disease (e.g. hazardous alcohol intake) as the prevalence of cirrhosis is increased in heavy drinkers with associated risk factors. The combination of haemochromatosis and heavy alcohol intake confers a very high risk of developing a HCC.

## 6.4. *Diagnosis of HCC:*

1. See surveillance recall policy and diagnostic algorithm (Figure 1)
2. In patients with known cirrhosis, HCC may be diagnosed on the basis of typical hallmark features (hypervascular in the arterial phase with washout in the portal venous or delayed phases) on one cross sectional dynamic imaging modality (4-phase multidetector CT scan or dynamic contrast-enhanced MRI). While only one imaging technique is required for nodules beyond 2 cm in diameter a more conservative approach with 2 techniques is recommended in suboptimal settings.
3. Much less emphasis is now given on the level of AFP as a diagnostic aid for HCC.
4. Needle biopsy of HCC is not recommended for patients who are candidates for potentially curative treatments. Biopsy for diagnostic confirmation should be considered for patients due to receive palliative systemic therapy and is usually required for recruitment to a systemic therapy clinical

trial. Biopsy may also be considered in patients undergoing palliative locoregional therapies (such as TACE), particularly in difficult cases (see Figure 1 – *Surveillance recall policy and diagnostic algorithm*). Needle biopsy carries a small risk of seeding tumour and may prevent future curative therapy such as liver transplantation. The risk of seeding may theoretically be reduced by performing the biopsy either laparoscopically or at the same time as ablation where the biopsy track is also ablated.

5. If patients are potential candidates for liver transplantation, biopsy should never be undertaken, unless at the express request of the Transplant Unit.

## 6.5. *Staging of HCC*

1. The optimum management of patients with HCC requires holistic assessment. This includes assessment of the tumour status (size and number of tumour deposits, position of tumour, presence of vascular invasion, and presence of extra-hepatic metastases), the severity of underlying liver disease (liver function – Child-Pugh staging, ascites and other complications of cirrhosis and portal hypertension), the aetiology of any underlying liver disease and ECOG patient performance status and co-morbidity.
2. The Barcelona Liver Clinic (BCLC) algorithm is recommended for prognostic prediction and treatment allocation and is endorsed by the AASLD and EASL-EORTC clinical guidelines. See: Figure 2.
3. Severity of liver disease is most commonly assessed by the Child-Pugh score. This may be calculated as in Table 1.
4. Portal hypertension is diagnosed by the presence of varices on endoscopic or sigmoidoscopic screening, or by surrogate measures, such as platelet count < 100,000/$mm^3$, ascites or splenomegaly.

## 6.6. *Surgical Resection*

### Indications:

1. Hepatic resection is the treatment of choice for HCC in non-cirrhotic livers.
2. Resection is the first-line treatment option for patients with solitary tumours and very well-preserved liver function, defined as normal bilirubin with either venous pressure gradient ≤10 mmHg or platelet count ≥100 000.
3. Additional indications for patients with multifocal tumours meeting Milan criteria (≤3 nodules ≤3 cm) or with mild portal hypertension not suitable for liver transplantation require prospective comparisons with locoregional treatments.

### Patient Selection

Selection of the ideal candidates involves an adequate assessment of the liver functional reserve and tumour extension. Assessment of liver function has moved from the gross determination of Child–Pugh class and may require measurement of indocyanine green retention rate at 15 min(ICG15) or hepatic venous pressure gradient (HVPG) ≥10 mmHg, as a direct measurement of relevant portal hypertension (or surrogate measures of portal hypertension; platelet count below 100,000/mm3 associated with splenomegaly).

Anatomical resections are recommended.

Neo-adjuvant or adjuvant therapies have not proven to improve outcome of patients treated with resection (or local ablation).

## 6.7. *Liver Transplantation*

### Patient Selection - Indications & Contraindications:

Liver transplantation is the first line treatment option for patients with single tumours less than 5 cm or ≤3 nodules ≤3 cm (Milan criteria) not suitable for resection.

Expanded UK criteria for listing patients with HCC for transplant are:

a. Single tumour ≤ 5cms diameter
b. Up to 5 tumours all ≤ 3cms or
c. Single tumour >5cms and ≤7cms diameter where there has been no evidence of tumour progression (volume increase by <20%) and no extrahepatic spread and no new nodule formation over a 6 month period.

Tumour rupture and an AFP >10,000 iu/ml are absolute contraindications to transplantation, as are extrahepatic spread and macroscopic vascular invasion. See also: *7.6 Liver Advisory Group on behalf of NHSBT – Liver Transplantation: Selection Criteria and Recipient Registration (March 2014)*

### Neoadjuvant locoregional therapy for transplant list patients

1. Locoregional therapy should be considered for all transplant list patients who have a hepatocellular carcinoma.
2. Patients out-with current proposed selection criteria will not be selectable on to the transplant list after their tumour has been downsized by surgical or locoregional treatments.

## 6.8. *Local Ablation:*

### Patient selection:

1. Local ablation with radiofrequency [RFA] is considered the standard of care for patients with BCLC 0-A tumours not suitable for surgery.
2. Child–Pugh A patients with non-surgical small tumours that are expected to achieve complete responses, are the ideal candidates for RFA. Treatment of patients with larger tumours (3–5 cm), multiple tumours (3 nodules <3 cm) and more advanced liver failure (Child–Pugh B) may be considered on an individual basis.

### Techniques:

1. RFA is usually performed radiologically, but may on occasion need combined radiological and (open or laparoscopic) surgical management for inaccessible lesions (e.g. lesions under the dome of the diaphragm, close to major vascular or biliary structures).
2. Advantages of RFA are that it is a shorter, less invasive treatment and may be better for patients with significant non-hepatic co-morbidity, as it does not usually require general anaesthetic. Ablation is associated with less post-procedure morbidity and less destruction of non-tumour affected liver. It may therefore be more suitable for patients with portal hypertension or moderate impairment of liver function (Child-Pugh B). The main disadvantage of ablation is that it does not routinely allow for sampling for histology. Where ablation is considered for a patient in whom the diagnosis is not definitive, biopsy of the lesion prior to ablation with further destruction of the biopsy track is recommended.
3. Ethanol injection may also be considered in cases where RFA is not technically feasible radiologically.

4. Microwave ablation has an important advantage compared to RFA, which is that treatment efficacy is less affected by vessels located in the proximity of the tumour, and it is being increasingly utilised. Other ablative therapies, such as laser ablation, irreversible electroporation or high intensity focussed ultrasound (HIFU) are still under investigation.
5. An open question is whether RFA can compete with surgical resection as a first-line treatment for patients with a small, solitary HCC.

## 6.9. *Chemoembolisation and other transcatheter therapies*

### Patient selection:

1. Chemoembolization is recommended for patients with BCLC stage B, multinodular asymptomatic tumours without vascular invasion or extrahepatic spread.
2. The best candidates are patients with preserved liver function (mostly Child–Pugh A or B7 without ascites). Gastroscopy should be performed in patients with a diagnosis of HCC where TACE is planned, to assess for oesophageal varices and the need for banding, prior to a procedure which may cause thrombocytopenia and thus result in a life-threatening bleed. Patients receiving doxorubicin as the chemotherapeutic agent should have a left ventricular ejection fraction >50%.
3. The benefits of chemoembolization should not be offset by treatment-induced liver failure. Chemoembolization is discouraged in patients with decompensated liver disease, advanced liver dysfunction, macroscopic invasion. Chemoembolisation is absolutely contraindicated in the presence of extrahepatic spread or main portal vein thrombosis but may be considered with minor segmental thrombosis.
4. The hepatoma arterial-embolisation prognostic (HAP) score predicts outcomes in patients with HCC undergoing TACE/TAE and may help guide treatment selection, allow stratification in clinical trials and facilitate meaningful comparisons across reported series (See: Table 6.2).

### Techniques:

1. Conventional chemoembolization (TACE) combines transcatheter delivery of chemotherapy emulsioned with lipiodol followed by vascular stagnation achieved with embolic agents. Chemoembolization achieves partial responses in 15–55% of patients, and significantly delays tumour progression and macrovascular invasion and provides a survival benefit.
2. There is no good evidence indicating which is the best chemotherapeutical agent (usually doxorubicin or cisplatin are given) and the optimal re-treatment strategy. Some of the best

response rates have been identified with a planned three cycle regime, with cycles occurring at time zero, two months and six months. Patients should be assessed between the first and second cycles for side effects and deterioration of liver function. Patients should receive CT scans six weeks after both the second cycle and final cycle to assess success. Patients without radiological evidence of success after the second cycle should be considered for systemic therapy.

3. Complications of TACE include deterioration of liver function and post-embolisation syndrome, where patient may experience right upper quadrant pain, pyrexia and signs of systemic inflammation in the first 7-10 days after treatment.
4. The use of drug-eluting beads (DC Bead©, Biocompatibles UK) has shown similar response rates to conventional TACE with gelfoam-lipiodol particles, but may be associated with less systemic adverse events. Their cost-effectiveness is unknown and their use can only be considered on an individual patient basis. Treatment outcomes may be more difficult to assess on standard cross-sectional imaging since lipiodol is not used with beads therapy.
5. Internal radiation with $^{131}$I or $^{90}$Y glass beads has shown promising anti-tumoural results with a safe profile, but cannot be recommended as standard therapy.

## 6.10. *Systemic therapy*

- Sorafenib, an orally active multikinase inhibitor that inhibits both tumour cell proliferation and angiogenesis, is the standard systemic therapy for HCC. It is indicated for patients with well-preserved liver function (Child-Pugh class A or B) and with advanced tumours (BCLC C) or those tumours progressing upon locoregional therapies. However, caution needs to be exercised in patients with Child-Pugh B status as the land-mark SHARP trial of sorafenib versus placebo in advanced HCC patients included 97% patients with Child-Pugh A status. Most phase III clinical trials in advanced HCC now only include Child-Pugh A patients with some second-line trials including Child-Pugh B7 patients also.
- Funding for sorafenib is gained via application to the NHS England National Cancer Drugs Fund. Criteria for funding are:
    1. Application made by and first cycle prescribed by a consultant specialist specifically trained and accredited in the use of systemic anti-cancer therapy
    2. HCC diagnosis
    3. Child-Pugh class A liver impairment or Child-Pugh class B with low disease burden
    4. No previous systemic therapy
    5. No role for surgery or after failure of surgery or after failure of locoregional therapy. Patients should be of performance status (PS) 0-2

- The usual initiation dose of sorafenib is 400mg twice daily. Patients with PS 2, Child-Pugh class B liver impairment or significant comorbidity may commence therapy at a reduced dose (typically 400mg once daily) with dose escalation if well tolerated. Patients are reviewed after 2 weeks and 4 weekly thereafter to assess side effects and suitability for continuing treatment. Common side effects include diarrhoea, fatigue, anorexia, blistering skin on hands and feet, hypertension, and proteinuria. Patients continue treatment until development of tumour progression or unacceptable side effects. Patients are generally staged every 12 weeks with CT-scans to ensure adequate tumour control.
- There is no standard second-line therapy for patients that have progressed on, or who are intolerant of, sorafenib. However, recruitment to a second-line clinical trial should be considered where available.
- Systemic chemotherapy, tamoxifen, immunotherapy, anti-androgen, and herbal drugs are not recommended for the clinical management of HCC patients.

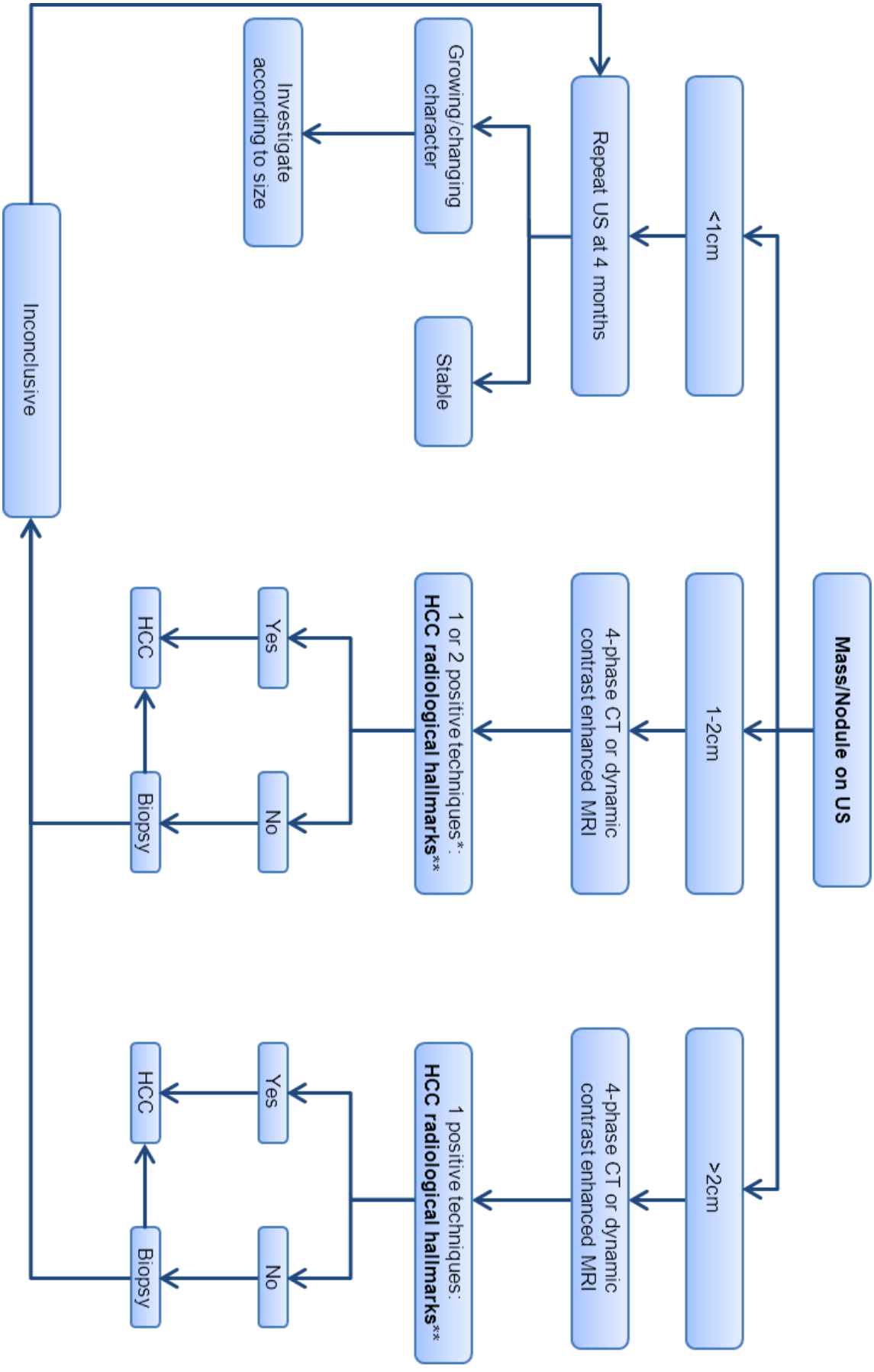
## 6.11. *Advanced disease:*

- Patients at BCLC D stage should receive palliative support (community Macmillan referral), including management of pain, nutrition and psychological support.

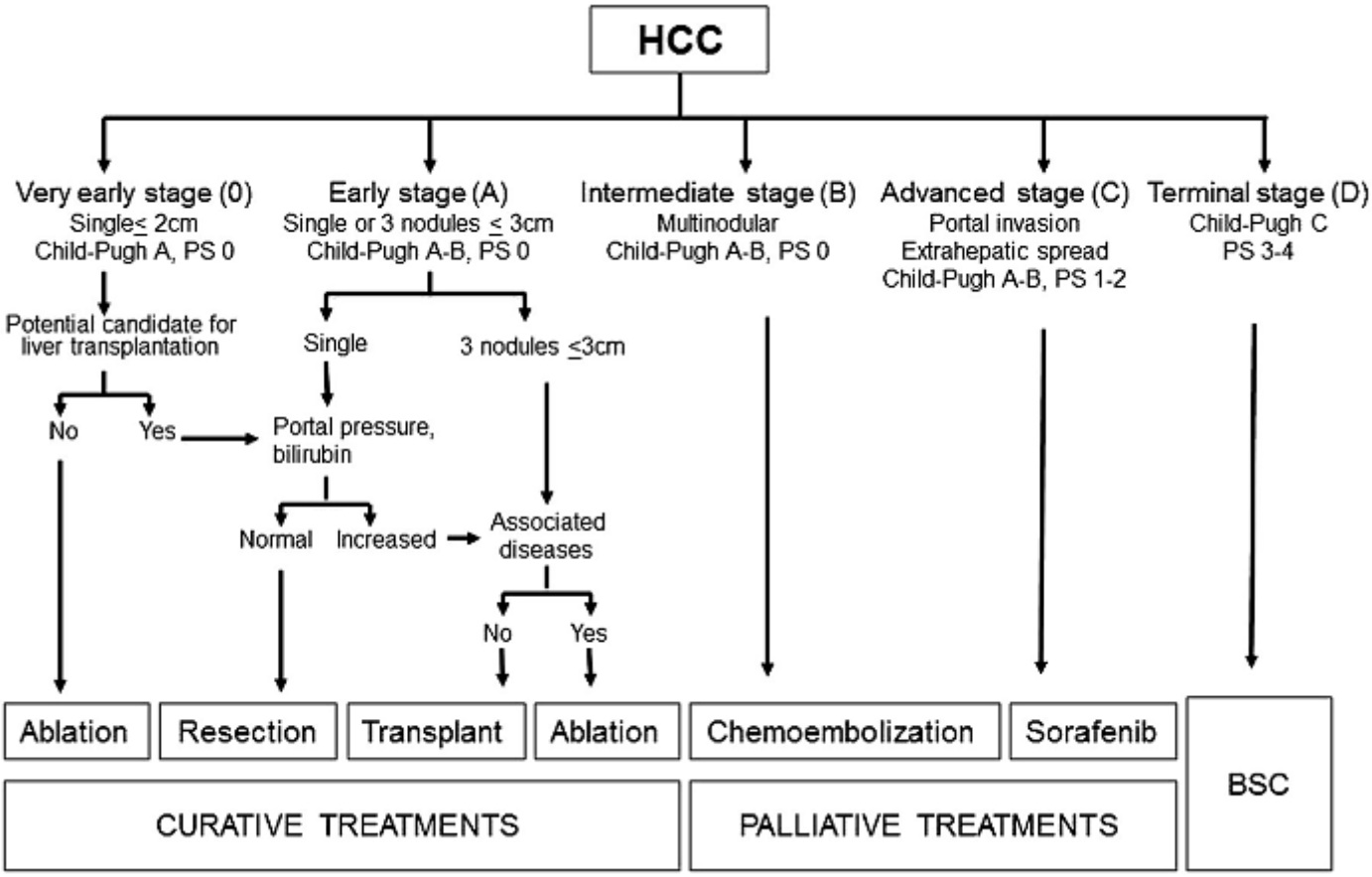
## 6.12. *Long term follow-up:*

- Patients who have had a good response to surgery, ablation or chemoembolisation should receive CT scans and alpha fetoprotein measurement on a minimum of a six monthly basis. Further treatment should be considered where appropriate for patients with evidence of recurrence.

## 6.13. *EASL-EORTC Surveillance recall policy and diagnostic algorithm*



## 6.14. *Barcelona Clinic Liver Cancer strategy for diagnosis and staging of HCC*




Patients are stratified into different stages according to tumour burden, liver function and physical status. Each stage is linked to the first-line treatment option that is proposed according to the available scientific evidence. It has to be stressed that the strategy applies for patients evaluated for hepatocellular carcinoma (HCC) and not for end-stage liver cirrhosis. If this is the case, patients should be evaluated for liver transplant and HCC diagnosis could merely become a contraindication if the enlisting criteria are exceeded. If transplant is not feasible, short-term prognosis is poor and HCC treatment will be of no benefit.

**Table 6.1: The Child-Pugh classification system for staging cirrhosis**

| Measure | 1 | 2 | 3 |
|---|---|---|---|
| Bilirubin (µmol/l) | <34 | 34-50 | >50 |
| Albumin (g/l) | >35 | 28-35 | <28 |
| PT prolongation (sec) ./ INR | <4 / <1.7 | 4-6 / 1.7-2.4 | >6 / >2.4 |
| Encephalopathy | none | Grade 1/2 | Grade 3/4 |
| Ascites | none | mild | marked |

Categories: A: total score 5-6
B: total score 7-9
C: total score 10-15

**Table 6.2: Calculation of the hepatoma arterial-embolisation prognostic (HAP) score**

| Prognostic factor | Points |
|---|---|
| Albumin < 36 g/dl | 1 |
| AFP > 400 ng/ml | 1 |
| Bilirubin > 17 µmol/l | 1 |
| Maximum tumour diameter >7 cm | 1 |

| HAP classification | Points |
|---|---|
| HAP A | 0 |
| HAP B | 1 |
| HAP C | 2 |
| HAP D | >2 |

## 6.15. *TNM classification and histopathology reporting proforma – HCC*

### TNM classification

**Primary**

pT0 No evidence of primary tumour

pT1 Solitary tumour without vascular invasion

pT2 Solitary tumour with vascular invasion or multiple tumours , none more than 5 cm in greatest dimension

pT3a Multiple tumours, any more than 5 cm

pT3b Single or multiple tumours of any size involving a major branch of the portal vein or hepatic vein

pT4 Tumour(s) with direct invasion of adjacent organs other than the gall bladder or with perforation of visceral peritoneum.

**N – Regional lymph nodes – all tumour sites**

pNx Regional lymph nodes cannot be assessed

pN0 No regional lymph node metastases. Histological examination of a regional lymphadenectomy specimen will ordinarily include three or more lymph nodes for HCC, ICC and gall bladder cancer, and 15 lymph nodes for perihilar CC. If the lymph nodes are negative, but the number ordinarily examined is not met, classify as pN0

pN1 Regional lymph node metastasis.

**M – Distant metastasis**

pM1 Distant metastasis. This includes metastasis to non-regional lymph nodes, including: periaortic, pericaval, superior mesenteric artery and/or coeliac artery lymph nodes (The only pM code that can be assigned by the pathologist is pM1 – it is not possible to ascertain the absence of distant metastases).

**Stage grouping – for hepatocellular carcinoma**

| | |
|---|---|
| Stage I | T1 N0 M0 |
| Stage II | T2 N0 M0 |
| Stage IIIA | T3a N0 M0 |
| Stage IIIB | T3b N0 M0 |
| Stage IIIC | T4 N0 M0 |
| Stage IVA | Any T N1 M0 |
| Stage IVB | Any T Any N M1 |

## 6.16. *Reporting proforma for liver resection: hepatocellular carcinoma*

Surname: ..... Forenames: ..... Date of birth: .....

Sex: ..... CHI/NHS no:..... Hospital: .....

Hospital no: ..... Date of receipt: ..... Date of reporting: .....

Report no: ..... Pathologist: ..... Surgeon: .....

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**Gross description**

**Type of specimen:** Segmental resection □ List segments (if known): ……

Non-anatomic (wedge) resection □ Site/segment of origin: …… Hepatectomy (at transplant) □

Specimen weight……g

For segmental resections, specimen dimensions:

antero-posterior ……mm, medio-lateral ……mm, supero-inferior……mm

Number of tumours present. …… List maximum tumour diameters (up to largest 4): ……mm

Satellite tumour(s) present: Yes □ No □

Distance from nearest hepatic resection margin: ……..mm

Macroscopic involvement of vessels Yes □ No □ If yes, diameter of vessel involved ……mm

Specify which vessel is involved: main left portal vein/main right portal vein/hepatic vein

Liver capsule intact and smooth Yes □ No □

Invasion of adherent or adjacent organ Yes □ No □ If yes, which organ …….....…..

Lymph node(s) received Yes □ No □

**Histology**

Tumour type: HCC NOS □ Fibrolamellar carcinoma □ Other histological type (specify)…….....

Tumour grade/differentiation by worst area: Well □ Moderate □ Poor □

Tumour cells present at margin Yes □ No □

If margin is clear: is clearance >10 mm: Yes □ No □

If no, minimum distance to margin ……mm

Macroscopic vascular invasion confirmed: Yes □ No □

Microscopic vascular invasion identified: Yes □ No □

Evidence of response to preoperative treatment: Yes □ No □ If yes, complete □ incomplete □

**Background liver**

**Fibrosis**

If present:

- None present □
- Not bridging □
- Bridging □
- Bridging with nodules □
- Complete cirrhosis □

**Aetiology**

- Hepatitis B □
- Hepatitis C □
- Autoimmune hepatitis □
- Haemochromatosis □
- Alcohol □
- NAFLD □
- Not known □

Other.....

Number of lymph nodes examined: …….. Number with metastases: …….

**Comments/additional information**

**Pathological staging pT…….. pN…….**

| | | | |
|---|---|---|---|
| PT0 | No tumour identified | | |
| pT1 | Solitary without vascular invasion | pN0 | No lymph node metastases |
| pT2 | Solitary with vascular invasion or multiple ≤50 mm | pN1 | Lymph node metastases |
| pT3a | Multiple, any ≥50 mm | | |
| pT3b | Involvement of major branch of portal or hepatic vein | | |
| pT4 | Invades adjacent organs (other than gall bladder) or perforates peritoneum | | |

**Signature of pathologist …….....** **Date …./…./……..**

**SNOMED codes** **pT ..…** **M …...**