Management of Hepatocellular Carcinoma

These guidelines are intended to represent the current position on diagnosis and management of patients with suspected or confirmed hepatocellular carcinoma (HCC) in Cambridge. They are intended to guide referring clinicians about current management algorithms. These guidelines are broadly based upon the EASL guidelines of 2012.

There will also be patients who fall outside of published guidelines. If there are any concerns or questions then please do not hesitate to contact a member of the primary liver lesion MDT.

Diagnosis of hepatocellular carcinoma

The diagnosis of HCC is based upon the current (2012) EASL guidelines (European Association For The Study Of The Liver/European Organisation For Research And Treatment Of Cancer, 2012). A biopsy is not necessary to establish the diagnosis. HCC can be diagnosed by either radiological OR pathological investigations. A normal AFP does not exclude the diagnosis of HCC as only specific transcriptional sub-types of HCC express AFP.

Radiological diagnosis

This is based upon the size of lesion and dynamic contrast characteristics on CT or MR (Figure 1). HCC can be diagnosed in the presence of arterial phase enhancement on CT or MR and portal venous / late phase washout using conventional contrast agents. Importantly, for initial investigation of nodules within a cirrhotic liver conventional gadolinium, and not Primovist, should be used.

Whilst MR imaging characteristics such as a T2 correlate or restricted diffusion on DWI are suspicious for HCC, they are not diagnostic.

Figure 1. Diagnostic algorithm for investigation of possible HCC in an abnormal liver. Adapted from EASL guidelines 2012
Pathological diagnosis

A liver biopsy is not required to establish or confirm a diagnosis of HCC in most cases. It is however, required when a patient with a liver lesion does not have clinching radiological dynamic contrast-characteristics.

Targeted biopsies of indeterminate lesions within a radiologically cirrhotic liver should only be carried out after discussion at the primary liver lesion multi-disciplinary team (MDT) meeting. All biopsies of HCC tissue should be reviewed centrally during the MDT process, including other relevant histological specimens, such as previous background liver biopsies.

Slides AND blocks should be forwarded to:
The HPB sub-specialty team
Box 235
Department of Histopathology
Addenbrooke’s Hospital
Cambridge
CB2 0QQ
When to refer

Lesion in a radiologically normal liver and no suspicion of background liver disease

Patients with a new lesion in a presumed normal liver can be initially managed at the referring centre. If the lesion is discovered on US scanning, then the patient will require cross-sectional imaging, ideally with a 4-phase MR scan. Clinical review should look to exclude risk factors for liver disease and check for a history of exogenous hormone usage. In general, if there remains diagnostic doubt (i.e. not clearly a haemangioma or FNH on MRI) then the next investigation would be a targeted, percutaneous biopsy AND biopsy of the background liver. If targeted biopsy is difficult or there are particular concerning features then please either discuss or refer to the primary liver lesion MDT.

Lesion in a radiologically abnormal liver or suspicion of background liver disease

Patients with a new lesion in this context have a higher likelihood of HCC. They should undergo cross-sectional imaging, ideally with MR and if there are positive hallmarks of HCC (see Figure 1) should be referred to the primary liver lesion MDT. Patients with Childs Pugh B or C liver disease should also be referred immediately as they may be candidates for transplantation.

No lesion in a radiological abnormal liver but elevated or rising AFP

Patients in this context may have an HCC that is not adequately seen by imaging. The first step is to ensure that the patient has undergone an optimal 3- or 4-phase cross-sectional study (ideally MR with conventional gadolinium). If doubt remains or there are particular concerning features then please either discuss or refer to the primary liver lesion MDT.
Management of hepatocellular carcinoma

General principles

The management of HCC is based upon the BCLC algorithm (Figure 2), incorporated into the current (2012) EASL guidelines (European Association For The Study Of The Liver/European Organisation For Research And Treatment Of Cancer, 2012). Critical for appropriate decision-making is the assessment of the patient along 3 separate axes:

2. Background liver function.
3. Number, size and vascular relationship of HCC lesions.

Patients should be assessed according to this algorithm and assigned to the most leftward treatment modality appropriate for their BCLC stage. Should treatment modalities be inappropriate (e.g. RFA not suitable for sub-capsular lesions) then treatment stage migration towards the right of the algorithm occurs. Radioembolisation or selective internal radiotherapy (SIRT) is a promising new therapy, but its use is limited to clinical trials or selected cases only.

Performance status

The performance status (PS) of the patient is critical in determination of prognosis in HCC (Hsu et al., 2013) and for appropriate treatment selection. It is based upon the ECOG system (http://ecog-acrin.org/resources/ecog-performance-status). The PS should be supplied at time of initial referral, in addition to all subsequent treatment decision-points.
Eastern Liver Network HCC guidelines v 3.3 March 2017

<table>
<thead>
<tr>
<th>ECOG Performance Status Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Fully active, able to carry on all pre-disease performance without restriction</td>
</tr>
<tr>
<td>1</td>
<td>Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work</td>
</tr>
<tr>
<td>2</td>
<td>Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours</td>
</tr>
<tr>
<td>3</td>
<td>Capable of only limited self-care, confined to bed or chair more than 50% of waking hours</td>
</tr>
<tr>
<td>4</td>
<td>Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair</td>
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</table>

Past medical history

The nature and severity of co-morbidities is critically important to the decision-making process at the Primary liver lesion MDT meeting. It is vitally important that this accompanies the initial referral to the MDT, where a clinician who has met the patient may well not be present.

Derogations from EASL guidelines

Our management of HCC in the East Anglian region derogates from the published EASL guidelines in the following situations:

1. Selection for consideration of liver transplantation is based on the Liver Advisory Group / NHSBT modification of the Milan criteria. Therefore, patients with a solitary HCC ≤5cm OR ≤5 separate lesions all ≤3cm OR exceptionally solitary lesions between 5 and 7cm that are stable in size over 6 months after locoregional therapy can be considered.

2. Both RFA and TAE are considered in patients with PS 1.

3. TAE is currently utilized in Cambridge, rather than TACE or DEB-TACE (Marelli et al., 2007; Meyer et al., 2013).

4. The status of branch portal vein invasion and thrombosis is controversial. Patients with branch PV thrombosis are not automatically assigned to BCLC C and are potential candidates for resection or TAE.

Treatment options for patients with hepatocellular carcinoma

Hepatic resection

For subjects with a single HCC of any size (BCLC 0 / A), curative resection is possible within strict inclusion criteria. The main considerations are:

1. The patient’s suitability for a potentially prolonged laparotomy / general anaesthesia.

2. The size of the proposed resection and predicted remnant liver volume.

3. The degree of background liver disease and the severity of pre-operative portal hypertension.

Inclusion criteria:

1. Single HCC (radiological or histological diagnosis); exceptionally patients with more than one tumour, localised to a single segment, may also be considered.

2. No main portal vein or IVC invasion on cross-sectional imaging.

3. No extrahepatic disease on CT of chest and abdomen.

4. No evidence of elevated portal pressure.
a. If radiological or histological diagnosis of cirrhosis, subject needs hepatic venous pressure studies to measure the HVPG, unless they are already known to have clinically significant portal hypertension i.e. varices. An HVPG ≥ 10mmHg usually precludes resection.

b. If no evidence of cirrhosis, then either percutaneous or trans-jugular biopsy of background liver is needed to confirm degree of hepatic fibrosis.

5. No significant co-morbidity that would preclude operation or anaesthesia.

6. The potential remnant liver volume must be sufficient to permit adequate liver function in the post-operative period. There is little evidence to guide specific amounts of permissible residual liver volume, but volumetry is undertaken and considered on an individual patient basis. Liver volumes can be calculated from either Addenbrooke’s or referring centre CT studies and are requested from the radiographers.

7. Portal vein embolization (PVE) to the same side as tumour may be considered to increase potential remnant liver volume. It has a limited role in those with background cirrhosis due to the inability of the cirrhotic liver to hypertrophy in response to PVE.

8. Adjuvant therapy is only utilized in the context of clinical trials.

Follow-up:

1. 4-monthly triple-phase cross-sectional imaging (CT / MR (standard gadolinium)) for the first year post-resection.
2. CT chest at 12 months post-resection.
3. 6-monthly triple-phase cross-sectional imaging (CT / MR (standard gadolinium)) for the second year post-resection.
4. Thereafter, 6-monthly surveillance imaging with either US, CT or MR dependent on MDT discussion.
5. AFP at each clinical encounter in all subjects to survey for recurrence and metachronous primary development.

Radiofrequency ablation (RFA)

For subjects with up to 3 HCCs, none of which is larger than 3cm on cross-sectional imaging (BCLC 0 / A), potentially curative treatment with RFA is possible. RFA can be performed as a purely percutaneous ultrasound-guided procedure, a laparoscopic-assisted procedure or under exceptional circumstances as an open procedure at laparotomy. It does require general anaesthesia and therefore the patient needs to be fit enough to undergo this.

Suitability for, and success of, RFA is critically dependent upon the tumor localisation. Considerations are:

1. Lesions close to the capsule of the liver increase the risk of post-ablation haemorrhage and are therefore unsuitable for percutaneous RFA if the probe cannot traverse normal liver before entering the tumour.
2. Major vessels can act as a heat-sink from the ablation and therefore decisions about lesions close to vessels are made on an individual basis.

Inclusion criteria:

1. Up to 3 HCC (radiological or histological diagnosis), none of which is larger than 3cm.
2. No vascular invasion on cross-sectional imaging.
3. No extrahepatic disease on CT of chest and abdomen.
4. No significant co-morbidity that would preclude anaesthesia.
5. Minimum coagulation parameters are platelets $\geq 50$ and a pro-thrombin (PT) time of $\leq 15$ seconds. Values outside of these will require correction.

**Follow-up:**

1. Triple-phase cross-sectional imaging (CT / MR (standard gadolinium)) 6 weeks after RFA.
2. 4-monthly triple-phase cross-sectional imaging (CT / MR (standard gadolinium)) for the first year post-ablation.
3. CT chest at 12 months post-ablation.
4. 6-monthly triple-phase cross-sectional imaging (CT / MR (standard gadolinium)) for the second year post-ablation.
5. Thereafter, 6-monthly surveillance imaging with either US, CT or MR dependent on MDT discussion.
6. AFP at each clinical encounter in all subjects to survey for recurrence and metachronous primary development.

**Liver transplantation**

Liver transplantation offers the possibility of cure of both background liver disease as well as hepatocellular carcinoma, within strict inclusion criteria. Listing criteria for patients with HCC are based upon a UK-modification to the Milan criteria (Mazzaferro et al., 1996). Patients with a solitary HCC $\leq 5$cm or up to 5 separate lesions all $\leq 3$cm (BCLC A) can be considered. Recent changes preclude the transplantation of patients with an AFP $\geq$1000 kU/L.

**Inclusion criteria:**

1. Solitary HCC $\leq 5$cm OR $\leq 5$ separate lesions all $\leq 3$cm (radiological or histological diagnosis).
2. Exceptionally solitary lesions between 5 and 7cm that are stable in size over 6 months after locoregional therapy can be considered.
3. AFP $\leq$1000 kU/L.
4. No vascular invasion on cross-sectional imaging.
5. No extrahepatic disease on CT of chest and abdomen.
6. No significant co-morbidity that would preclude anaesthesia or transplantation.

**Waiting list management:**

1. 3-monthly triple-phase cross-sectional imaging (CT / MR (standard gadolinium)) to ensure remains within criteria.
2. 6-monthly CT chest.
3. AFP at each clinical encounter in all subjects.
4. In subjects with preserved liver function (Childs Pugh A), loco-regional therapy with RFA or TAE can be considered on an individual basis.

**Follow-up:**

1. 6-monthly triple-phase cross-sectional imaging (CT / MR (standard gadolinium)) for 4 years post-transplantation for subjects with any of these adverse tumour features:
   a. Any vascular invasion.
   b. Poor differentiation grade.
c. AFP-positive tumour (AFP ≥10kU/L) at transplantation.

2. AFP at each clinical encounter in all subjects with an AFP-positive tumour (AFP ≥10kU/L) at transplantation.

3. Subjects without any of these features have no post-transplant surveillance.

**Trans-arterial embolisation / chemo-embolisation (TAE / TACE)**

Locoregional therapy with TAE is possible for patients with solitary or multifocal HCC without major vessel invasion (BCLC A / B). TAE should be seen as a course of treatment, with some lesions requiring multiple episodes of embolisation over time.

Outcomes are significantly worse for subjects with impaired liver function and therefore only subjects with Childs Pugh B7 or better, with no ascites can be considered. Initial treatment decisions are based on the hepatoma arterial-embolisation prognostic (HAP) score that incorporates an assessment of background liver function and tumour biology and is detailed below.

**Inclusion criteria:**

1. Solitary OR multi-focal HCC (radiological or histological diagnosis) with no lesion ≥ 7cm.

2. No vascular invasion on cross-sectional imaging. Branch portal venous invasion / thrombosis is a controversial area with little evidence to guide treatment. These patients will can be treated on an individual basis.

3. No extrahepatic disease on CT of chest and abdomen.

4. No main portal venous thrombosis; fugal portal venous flow is a relative contra-indication.

5. Childs Pugh ≤ B7.

6. Minimum coagulation parameters are platelets ≥50 and a pro-thrombin (PT) time of ≤15 seconds. Values outside of these will require correction.

7. Maintained renal function. Patients with an eGFR (Cockcroft-Gault) of ≥90 will undergo conventional TAE; patients with an eGFR of between 60 and 90 will undergo modified TAE with pre-hydration and use of visipaque contrast. Patients outside of this range will be treated on an individual basis, but TAE may lead to significant worsening of renal function.

Where TAE is to be utilized to prevent haemorrhage from exophytic or ruptured HCC, it is permissible to perform this outside of these size and metastases guidelines on an individual patient basis.
**Initial TAE treatment decisions, the HAP score:**

The HAP score was developed from a retrospective analysis of UK patients undergoing TAE / TACE, in order to identify predictors of survival, prior to the first episode of embolization (Kadalayil et al., 2013). It assigns one point to each of the following characteristics:

1. Albumin <36g/L
2. Bilirubin >17 μmol/L
3. AFP >400kU/L
4. Size of dominant tumour >7cm

Patients are classified into classes A to D by a points score of 0, 1, 2 >2 respectively. Survival analysis of these classes reveals significant differences with a median survival of 28 months, 19 months, 9 months and 4 months respectively (see Fig. 3).

![Figure 3](image)

**Re-treatment with TAE decisions, the ART score:**

The assessment for re-treatment with TACE (ART) score was developed from a retrospective analysis of Austrian patients after their first episode of TACE, in order to identify parameters of clinical and treatment response that predict survival after the second episode of embolization (Sieghart et al., 2013).

Points are assigned for worsening of liver function (assessed by Childs-Pugh score), a > 25% rise in AST and lack of radiological tumour response by EASL criteria. Radiological responses are graded according to the EASL criteria: complete response and partial response are grouped as radiological response; stable or progressive disease are grouped as no radiological response.

**Table 1.** Multi-variate analysis of survival by clinical and radiological criteria after first episode of TACE in an Austrian cohort (n = 107). From Sieghart et al, Hepatology, 2013.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Overall Survival</th>
<th>ART Score Points*</th>
<th>P-value (Cox Regress)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>95% CI</td>
<td>B</td>
</tr>
<tr>
<td>Child-Pugh score increase</td>
<td>Absent</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>+ 1 point</td>
<td>2.0</td>
<td>1.2-3.5</td>
<td>0.71</td>
</tr>
<tr>
<td>+ ≥2 points</td>
<td>4.4</td>
<td>2.0-9.6</td>
<td>1.49</td>
</tr>
<tr>
<td>AST increase ÷25%</td>
<td>Absent</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>8.4</td>
<td>4.5-15.5</td>
<td>2.13</td>
</tr>
<tr>
<td>Radiologic tumor response</td>
<td>Present</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>1.7</td>
<td>1.1-2.6</td>
<td>0.51</td>
</tr>
</tbody>
</table>

A score of ≥2.5 was associated with a significantly worse survival after second episode of TACE.
After the first episode of TAE a 6-week cross-sectional imaging study will be scored according to mRECIST criteria (see below) to adjudge treatment response to guide re-treatment decisions. Patients with an ART score of ≥2.5 will only exceptionally undergo re-treatment with further embolization.

**Follow-up:**

1. Triple-phase cross-sectional imaging (CT / MR (standard gadolinium)) and LFTs including AST 6 weeks after TAE.
2. Re-assess clinical status, liver function and tumour response.
3. If no further TAE required then 4-monthly triple-phase cross-sectional imaging (CT / MR (standard gadolinium)) for the first year post-TAE.
4. CT chest at 12 months post-TAE.
5. 6-monthly triple-phase cross-sectional imaging (CT / MR (standard gadolinium)) for the second year post-TAE.
6. Thereafter, 6-monthly surveillance imaging with either US, CT or MR dependent on MDT discussion.
7. AFP at each clinical encounter in all subjects to survey for recurrence and metachronous primary development.
**Sorafenib**

For subjects with bulky disease, major vessel invasion, metastases or clear evidence of disease progression despite previous therapies systemic therapy with sorafenib is appropriate (BCLC B / C).

The major consideration is the underlying liver function; patients beyond Childs Pugh B7 are not suitable for treatment.

Sorafenib can be provided at several hospitals within the East Anglian Region. Where feasible patients will be enrolled in current clinical trials.

**Inclusion criteria:**

1. Childs Pugh ≤B7.
2. Performance status 0 / 1.
3. No significant cardiovascular co-morbidity.

**Reporting of cross-sectional imaging after locoregional therapy for HCC**

Patients treated with locoregional therapy, such as RFA and TAE, undergo interval cross-sectional imaging with 3 or 4-phase CT or MR imaging respectively. As the size of residual lesion does not necessarily reflect residual disease in HCC, the scans should be reported according to the mRECIST criteria (Lencioni and Llovet, 2010). These criteria rely on the **maximum diameter of arterial enhancement**, rather than absolute lesion size and have been demonstrated to show significantly enhanced prognostic value that when compared to RECIST 1.1 criteria in patients with HCC treated with TAE (Gillmore et al., 2011).

The mRECIST response of each individual tumour will be used to guide re-treatment decisions.

1. Each lesion should be arterially-enhancing on the baseline cross-sectional imaging.
2. Measurement should be obtained on arterial phase CT or MR imaging.
3. We use a modified mRECIST strategy where a response is reported for each intrahepatic lesion according to the following scheme:

<table>
<thead>
<tr>
<th>mRECIST response</th>
<th>The disappearance of all intratumoral arterial enhancement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partial response</td>
<td>Reduction of &gt;30% of maximum arterial-enhancing diameter</td>
</tr>
<tr>
<td>Stable disease</td>
<td>A reduction of &lt;30% to an increase of &gt;20% of maximum arterial-enhancing diameter</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>Increase of &gt;20% of maximum arterial-enhancing diameter</td>
</tr>
</tbody>
</table>

4. After treatment large lesions can have significant areas of necrosis; the axis chosen for measurement should not include significant intervening areas of necrosis.
5. Some patients will have unmeasurable disease with hypovascular HCC, poorly defined or infiltrative tumours and will not be suitable for mRECIST reporting.
Follow-up:

- Triple-phase cross-sectional imaging (CT / MR (standard gadolinium)) 3-monthly whilst receiving sorafenib.

It is currently unclear whether regorafenib will be funded as a second-line therapy in cases of progression on sorafenib therapy.

Radio-embolisation / Selective internal radiotherapy (SIRT)

The place of SIRT in the management of HCC is yet to be established through randomized controlled trials and therefore remains available through clinical trials only or on a named-patient basis. It shows significant promise in patients with difficult disease patterns:

1. Large solitary lesions unsuitable for resection and too large for TAE.
2. Bulky bilobar disease unlikely to respond to TAE; these may require staged therapy to each lobe sequentially.
3. Disease refractory to treatment with TAE.
4. Main trunk portal vein thrombosis.

Inclusion criteria:

1. Childs Pugh ≤B7.
2. Performance status 0 / 1.
3. No significant cardiovascular co-morbidity.
4. No significant shunting to the lungs on planning angiogram or NM shunt study.

Follow-up:

1. Triple-phase cross-sectional imaging (CT / MR (standard gadolinium)) 6 weeks after SIRT.
2. 4-monthly triple-phase cross-sectional imaging (CT / MR (standard gadolinium)) for the first year post-SIRT.
3. CT chest at 12 months post-SIRT.
4. 6-monthly triple-phase cross-sectional imaging (CT / MR (standard gadolinium)) for the second year post-SIRT.
5. Thereafter, 6-monthly surveillance imaging with either US, CT or MR dependent on MDT discussion.
6. AFP at each clinical encounter in all subjects to survey for recurrence and metachronous primary development.

Palliative care

Palliative care is the active total care of patients whose disease is not responsive to curative treatment. Control of pain, other symptoms and caring for the psychological, social and spiritual aspects of life are paramount. The goal of palliative care is achievement of the best quality of life for patients and their carers.

Patients can be referred to either hospital specialist or community specialist palliative care teams at they or their family’s request or if an involved health care professional feels they would benefit from symptom management of pain and any other physical symptoms, psychological support (for patient, family or informal carers) and consideration of future care planning.
References


