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 2018 (European Association For The Study Of The Liver 2018).

There will 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 HCC

The diagnosis of HCC is based upon the current (2018) EASL guidelines (European Association For The Study Of The Liver 2018). A biopsy is not necessary to establish the diagnosis of HCC in a cirrhotic liver. HCC can be diagnosed by either radiological **OR** pathological investigations. A normal AFP does not exclude the diagnosis of HCC as only specific molecular sub-types of HCC express AFP.

Radiological diagnosis

Diagnosis of HCC can be made in a cirrhotic liver based upon the dynamic contrast characteristics of liver lesions on cross-sectional imaging (Figure 1). Importantly, for initial investigation of nodules within a cirrhotic liver conventional gadolinium, and not hepatobiliary contrast agents, should be used (as this increases the number of phases within which 'washout appearance' can be determined). We utilise the Li-RADs system to express diagnostic certainty based upon radiological features (Chernyak et al. 2017; Chernyak et al. 2018), on a scale from 1 – 5 of increasing concern for HCC.

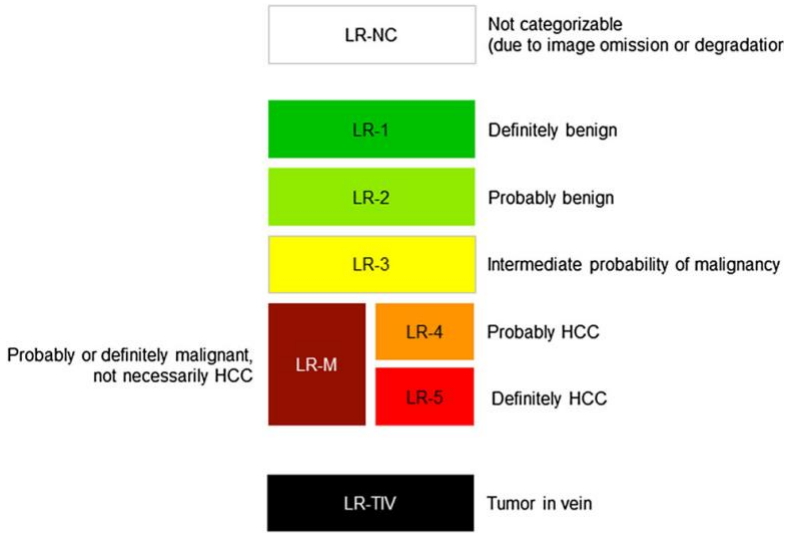


***Figure 1. Li-RADs Diagnostic categories based on cross-sectional imaging of a cirrhotic liver* (Chernyak et al. 2017).**

Assignment to a Li-RADs category is determined by the lesion size, presence or absence of arterial-phase hyperenhancement (APHE), portal or late phase washout and threshold growth. Threshold growth is defined as >50% size increase within a 6 month period (Figure 2) (Chernyak et al. 2018).

Eastern Liver Network HCC guidelines 2019

Arterial phase hyperenhancement (APHE)		No APHE		APHE (not rim)		
Observation size (mm)		< 20	≥ 20	< 10	10-19	≥ 20
Count major features: • "Washout" (not peripheral) • Enhancing "capsule" • Threshold growth	None	LR-3	LR-3	LR-3	LR-3	LR-4
	One	LR-3	LR-4	LR-4	LR-4 / LR-5	LR-5
	≥ Two	LR-4	LR-4	LR-4	LR-5	LR-5

LR-4 / LR-5

Observations in this cell are categorized LR-4, except:
- LR-5g, if ≥ 50% diameter increase in < 6 months (equivalent to OPTN 5A-g)
- LR-5us, if "washout" and visibility at screening ultrasound (per AASLD HCC criteria)

Figure 2. Li-RADS diagnostic table based upon imaging features.

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

A Li-RADs 5 lesion does not require a biopsy as this can be radiologically diagnosed as HCC. A Li-RADs 4 lesion will either require interval imaging or a biopsy for definitive diagnosis. The only instance where a Li-RADs 5 lesion will require biopsy is to access systemic therapies, such as sorafenib, where tissue diagnosis is currently mandatory (Figure 3).

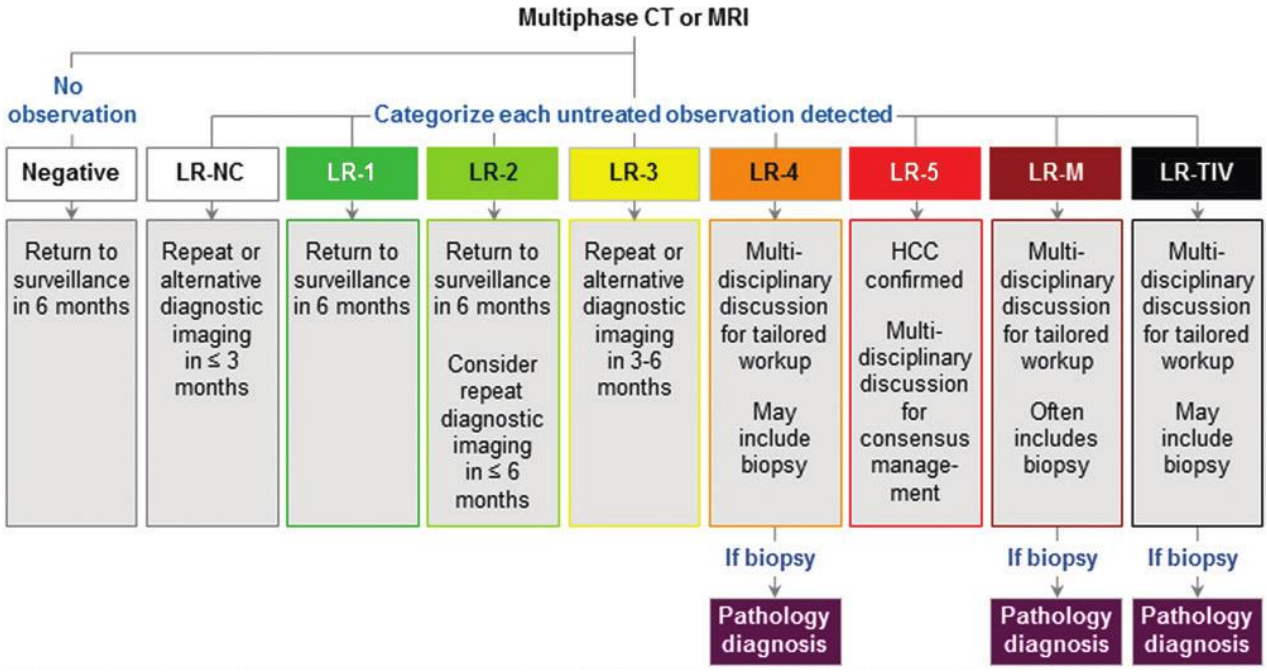


Figure 3. Standard management algorithm based upon Li-RADs category of liver lesions(Chernyak et al. 2018).

Pathological diagnosis

A liver biopsy is not required to establish or confirm a diagnosis of HCC in patients with cirrhosis or advanced liver disease. It is however, required when a patient with a liver lesion does not have clinching radiological dynamic contrast-characteristics or when the patient is not thought to have background liver disease.

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.

When to refer to the primary liver lesion MDT

1. 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.

2. 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 features of HCC (see above) 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 liver transplantation.

3. 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.

Minimum data required at time of referral

1. Dynamic cross-sectional imaging of the liver

An ultrasound or single-phase CT / MR are insufficient for assessment of the liver. Unless there are clear reasons, the patient must have undergone dynamic contrast enhanced cross-sectional imaging of the liver. Ideally, as per the LiRADs recommendations, for CT 4-phase imaging of the liver is used (pre, late arterial, portal and 3-5 minute delayed phases).

2. Medical history, including assessment of performance status

This is critical to determine candidacy for further investigation and different treatment options. Please send a complete medical history, an assessment of background liver disease and function as well as an assessment of the ECOG performance status.

3. Blood tests, including AFP and CA19-9

This is crucial to an understanding of the patients underlying liver function and therefore suitability for investigation and treatment.

4. What the patient knows

As cancer pathways become shorter it is sometimes necessary to telephone the patient to arrange further investigations or clinic visits. It is vital that we understand what the patient knows at the time of MDT referral.

Management of HCC

General principles

The management of HCC is based upon the BCLC algorithm (Figure 4), incorporated into the current EASL guidelines (European Association For The Study Of The Liver 2018). Critical for appropriate decision-making is the assessment of the patient along 3 separate axes:

1. Co-morbidities, performance status and patient preferences regarding further investigations or treatment.
2. Background liver function.
3. Number, size and vascular relationship of HCC lesions.

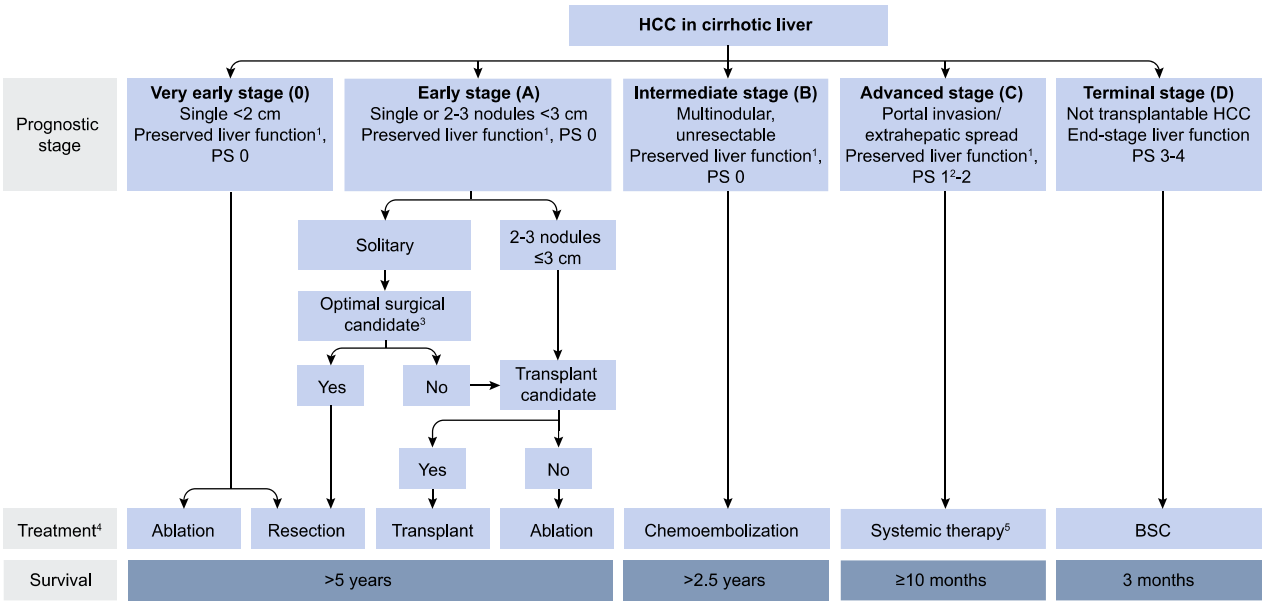


Figure 4. BCLC algorithm and treatment strategy*(European Association For The Study Of The Liver 2018). *Preserved liver function refers to Child Pugh B7 or better, with no ascites. In the UK we can consider transplantation in the context of up to 5 lesions (see liver transplant section).

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.

Performance status

The performance status (PS) of the patient is critical in determining 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.

ECOG Performance Status Grade	
0	Fully active, able to carry on all pre-disease performance without restriction
1	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
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair

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 utilised 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.
5. Access to systemic therapies in the UK requires a tissue diagnosis as mandated by NIHCE.

Curative therapies

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 so where feasible these patients should be referred to CUH for consideration.

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 CT-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 ≥ 50 and a pro-thrombin (PT) time of ≤ 15 seconds. Values outside of these will require correction.

Follow-up:

1. Adjuvant therapy is only utilized in the context of clinical trials so where feasible these patients should be referred to CUH for consideration of trials.
2. Cross-sectional imaging (CT (quad phase) / MR (standard gadolinium)) 6 weeks after RFA. For CT, pre contrast imaging is essential to assess background lesional hyperdensity.
3. 4-monthly cross-sectional imaging (CT quad phase / MR (standard gadolinium)) for the first-year post-ablation.
4. CT chest at 12 months post-ablation.
5. 6-monthly cross-sectional imaging (CT quad phase/ MR (standard gadolinium)) for the second-year post-ablation.
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.

Liver transplantation

Liver transplantation offers the possibility of cure of both background liver disease as well as HCC, 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 ≤5cm or up to 5 separate lesions all ≤3cm (BCLC A) can be considered. Recent changes preclude the transplantation of patients with an AFP ≥1000 kU/L.

Inclusion criteria:

1. Solitary HCC ≤5cm OR ≤5 separate lesions all ≤3cm (radiological or histological diagnosis) on 2 different imaging techniques.
2. Exceptionally solitary lesions between 5 and 7cm that are stable in size over 6 months after locoregional therapy can be considered.
3. AFP ≤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.

Down-staging:

Some patients beyond UK transplant criteria at time of presentation could be eligible for later consideration of transplantation if they undergo surgical or locoregional treatment reducing their tumour burden, under the down-staging criteria. This is applicable to patients with tumours that exceed current transplant criteria on tumour size, tumour number and serum AFP level. The following patients are excluded from consideration of transplantation under the down-staging pilot:

1. Macrovascular invasion – identified at any time on radiological imaging or liver resection pathology
2. Nodal or extrahepatic metastases at any time.
3. Ruptured HCC at any time.

Waiting list management:

1. 3-monthly dynamic contrast-enhanced cross-sectional imaging (CT / MR (standard gadolinium)) to ensure tumour configuration remains within transplant 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 / B7), loco-regional therapy with RFA or TAE can be considered on an individual basis.

Follow-up post-transplant:

1. 6-monthly cross-sectional imaging (CT triphasic; pre, late arterial and portal phases / MR (standard gadolinium)) for 4 years post-transplantation ONLY 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 time of transplantation.
2. AFP at each clinical encounter ONLY in subjects with an AFP-positive tumour (AFP ≥10kU/L) at time of transplantation.
3. Subjects without any of these features have no post-transplant surveillance.

Locoregional therapies

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: (1) non-curative; (2) 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 (see box 1).

Inclusion criteria:

a. Solitary OR multi-focal HCC with no lesion ≥ 7cm.

b. 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.

c. No extrahepatic disease on imaging of chest and abdomen.

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

e. Childs Pugh ≤ B7 with no ascites.

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

g. 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.

Where feasible, these patients should be considered and referred to CUH for clinical trials.

Box 1: 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 *Figure 5*).

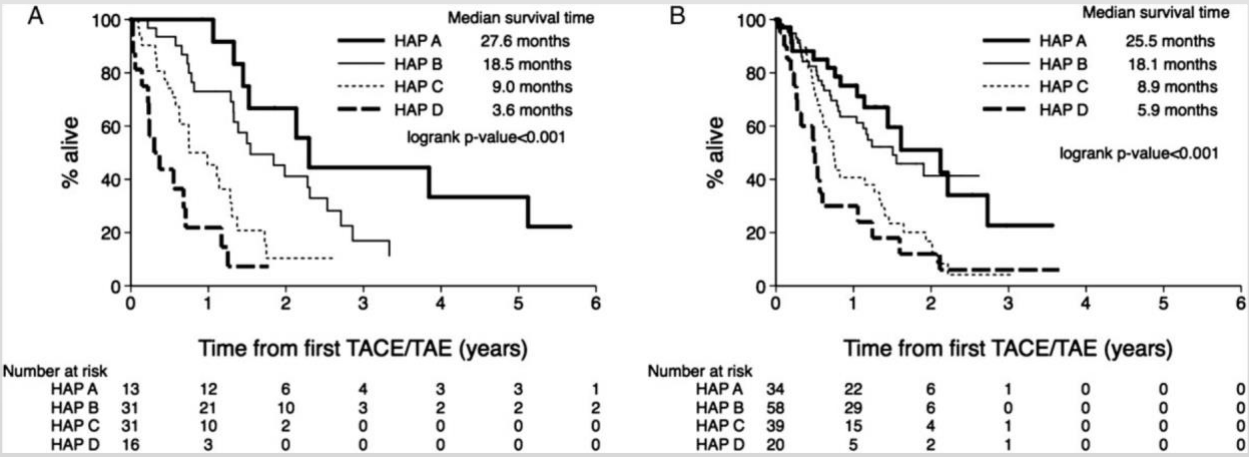


Figure 5. Kaplan Meier survival analysis of patients after first episode of TAE / TACE stratified by pre-TACE HAP score in the derivation cohort (left, n = 114) and validation cohort (right, n = 166). From Kadayil et al, Annals of Oncology, 2013.

Patients with a HAP score of >2 (Class D) should only exceptionally be treated with TAE.

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: (1) worsening of liver function (assessed by Childs-Pugh score); (2) a > 25% rise in AST and; (3) lack of radiological tumour response as defined by 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.

Variable		Overall Survival HR	95% CI	B	ART Score Points*	*P*-value (Cox Regression)
Child-Pugh score increase	Absent	1			–	
	+ 1 point	2.0	1.2-3.5	0.71	1.5	
	+ ≥2 points	4.4	2.0-9.6	1.49	3	<0.001
AST increase >25%	Absent	1			–	
	Present	8.4	4.5-15.5	2.13	4	<0.001
Radiologic tumor response	Present	1			–	
	Absent	1.7	1.1-2.6	0.51	1	0.026

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 Li-RADs(Chernyak et al. 2018) or mRECIST criteria (Lencioni & Llovet 2010) (see Box 2) 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:

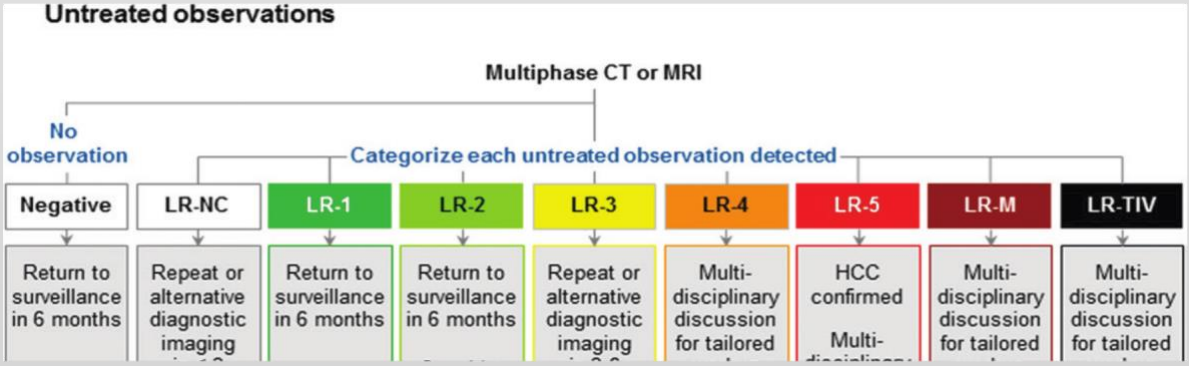
1. Cross-sectional imaging (CT quad phase / MR (standard gadolinium)) and LFTs, including AST, 6 weeks after TAE. For CT, pre contrast imaging is essential to assess background lesional hyper density.
2. Re-assess clinical status, liver function and tumour response.
3. If no further TAE required then 4-monthly cross-sectional imaging (CT quad phase / MR (standard gadolinium)) for the first year post-TAE.
4. CT chest at 12 months post-TAE.
5. 6-monthly cross-sectional imaging (CT quad phase / 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.

Box 2: Reporting of treatment response after locoregional therapy for HCC

Patients treated with locoregional therapy, such as RFA and TAE, undergo interval cross-sectional to adjudge tumour response. As the size of residual lesion does not necessarily reflect residual disease in HCC, the scans should be reported according to the Li-RADs (Chernyak, V. et al., 2018) or mRECIST criteria11 (European Association For The Study Of The Liver, 2018). Both of these criteria rely on the **maximum diameter of arterial enhancement**, rather than absolute lesion size and in the case of mRECIST have been demonstrated to show significantly enhanced prognostic value that when compared to RECIST 1.1 criteria in patients with HCC treated with TAE (Sieghart, W. et al., 2013).

1. Li-RADs

a. Li-RADs is used for routine response reporting and clinical management
b. The treatment response of each individual lesion is reported, based upon the presence of APHE or washout.



2. mRECIST

The mRECIST response is usually used in the context of clinical trials.

a. mRECIST is usually applied to the whole liver rather than individual lesions. We use a modified mRECIST strategy where a response is reported for **each** intrahepatic lesion according to the following scheme:

mRECIST response	
Complete response	The disappearance of all intratumoral arterial enhancement
Partial response	**Reduction of >30%** of maximum APHE diameter
Stable disease	A reduction of <30% to an increase of >20% of maximum APHE diameter
Progressive disease	**Increase of >20%** of maximum APHE diameter

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

Radio-embolisation / Selective internal radiotherapy (SIRT)

The place of SIRT in the management of HCC is not established and recent randomized controlled trials have shown no benefit for SIRT when compared to sorafenib therapy (Vilgrain et al. 2017; Chow et al. 2018).

Therefore, SIRT is utilised only through clinical trials or on a named-patient basis. It may have a role 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. Liver-localised disease
2. Childs Pugh ≤B7.
3. Performance status 0 / 1.
4. No significant cardiovascular co-morbidity.
5. No significant shunting to the lungs on planning angiogram or NM shunt study.

Follow-up:

1. Cross-sectional imaging (CT quad phase / MR (standard gadolinium)) 6 weeks after SIRT.
2. 4-monthly cross-sectional imaging (CT quad phase / MR (standard gadolinium)) for the first year post-SIRT.
3. CT chest at 12 months post-SIRT.
4. 6-monthly cross-sectional imaging (CT quad phase / 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.

1st line systemic therapies

Sorafenib and lenvatinib

For subjects with bulky disease, major vessel invasion, metastases or clear evidence of disease progression despite previous loco-regional therapies (BCLC B / C), systemic therapy with sorafenib (tyrosine kinase inhibitor (TKI) of VEGR, PDGFR and Raf) or lenvatinib (TKI against VEGFR1-3, FGF1-4, PDGF. RET, KIT) are appropriate in the first-line treatment setting based on randomized phase III data from the SHARP trial and REFLECT trials respectively. The SHARP trial showed median survival was 10.7m in sorafenib treated patients compared with 7.9 m in placebo group, and improved median time to progression, 5.5m vs 2.8 m (Llovet et al. 2008). The REFLECT trial showed lenvatinib was non-inferior to sorafenib in overall survival (13.6 m for levantinib vs 12.3m for sorafenib) with improvements in secondary endpoints of progression-free survival (7.4m vs 3.7m), time to progression (8.9m vs 3.7m) and objective response (24% vs 9%) (Kudo et al. 2018).

The major consideration is the underlying liver function; patients should be Childs Pugh A to be eligible for Cancer Drug Fund applications for either sorafenib or lenvatinib.

Where feasible, patients will be enrolled in available current clinical trials at CUH or in London.

Inclusion criteria:

1. Childs Pugh ≤A6
2. ECOG performance status 0 - 2 for sorafenib, 0 - 1 for lenvatinib.
3. No significant cardiovascular co-morbidity.
4. The patient has a confirmed histological diagnosis of hepatocellular carcinoma. OR a biopsy is deemed to be very high risk or technically not feasible in the patient AND the following criteria are met:

   Option 1: The decision not to biopsy has been made and documented by a specialist HCC MDM.
   Option 2: The tumour meets the non-invasive diagnostic criteria of hepatocellular carcinoma*

   It is expected that option 2 will only apply in exceptional circumstances and it should be noted that audit of non-biopsy rates will be reviewed regularly.

   *EASL–EORTC Clinical Practice Guidelines: Management, Journal of Hepatology 2012 vol. 56 p 908–943. Non-invasive criteria can only be applied to cirrhotic patients and are based on imaging techniques obtained by 4-phase multidetector CT scan or dynamic contrast-enhanced MRI. Diagnosis should be based on the identification of the typical hallmark of HCC (hypervascular in the arterial phase with washout in the portal venous or delayed phases). While one imaging technique is required for nodules beyond 1 cm in diameter a more conservative approach with 2 techniques is recommended in suboptimal settings.

Follow-up:

1. Dosing and toxicity management as per Summary of Product Characteristics for sorafenib and lenvatinib. Note the differing starting doses of lenvatinib according to the patient body weight being above or below 60Kg.
2. No treatment breaks of more than 6 weeks beyond the expected cycle length are allowed (to allow any toxicity of current therapy to settle or intercurrent comorbidities to improve).
3. Cross-sectional imaging (CT quad phase / MR (standard gadolinium)) 3-monthly whilst receiving TKI.
4. The treatments are continued until loss of clinical benefit or unacceptable toxicity or patient choice to stop treatment.

2nd line systemic therapies

Where feasible, patients who may be suitable for systemic therapies in the 2nd line setting and beyond will be enrolled in available current clinical trials at CUH or in London.

In the standard of care setting, regorafenib (TKI to VEGFR and TIE2) is approved for patients with HCC who progressed on sorafenib treatment based on data from the RESORCE trial showing improved overall survival versus placebo, median survival 10.6 m vs 7.8m, hazard ratio 0.63 (Bruix et al. 2016). There is no efficacy and toxicity data for regorafenib in patients previously treated with sorafenib who had to either discontinue sorafenib on account of toxicity or were unable to tolerate total daily doses of sorafenib of 400mg or more.

Inclusion criteria (for CDF application):

1. Childs Pugh ≤A6
2. ECOG performance status 0 / 1
3. The only other TKI with which the patient has been previously treated is sorafenib.

Follow-up:

1. Dosing and toxicity management as per Summary of Product Characteristics for regorafenib
2. No treatment breaks of more than 6 weeks beyond the expected cycle length are allowed (to allow any toxicity of current therapy to settle or intercurrent comorbidities to improve).
3. Cross-sectional imaging (CT quad phase / MR (standard gadolinium)) 3-monthly whilst receiving TKI.
4. The treatments are continued until loss of clinical benefit or unacceptable toxicity or patient choice to stop treatment.

Palliative care

Patients may have supportive and or palliative care needs as a consequence of their hepatocellular carcinoma, underlying advanced liver disease or another pathology. Their needs and preferences should be regularly reviewed and onward referrals for symptom management, psychological support and future care planning if needs exceed that which can be provided by involved primary health care team, hepatology and or oncology clinicians made when appropriate.

References

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