**Hepatocellular carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up**

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**incidence**

Hepatocellular carcinoma (HCC) is the fifth most common cancer in men and eighth most common cancer in women worldwide, resulting in at least 500 000 deaths per year. It accounts for 90% of all liver cancers. Its crude incidence in the European Union is 8.29/100 000. Areas such as Asia and sub-Saharan Africa with high rates of infectious hepatitis have incidences as high as 120 cases per 100 000. It is four to eight times more common in men and usually associated with chronic liver injury [hepatitis B (HBV), hepatitis C (HCV) and alcoholic cirrhosis]. Chronic infection with HBV in the setting of cirrhosis increases the risk of HCC 100-fold. Some 5%–30% of individuals with HCV infection develop chronic liver disease, ~30% progress to cirrhosis, and in these, 1%–2% per year develop HCC. Co-infection with HBV further increases the risk. Alcohol abuse in the setting of chronic HCV infection doubles the risk of HCC compared with HCV infection alone. Median age at diagnosis is between 50 and 60 years. In Africa and Asia, age at diagnosis is substantially younger, the cancer occurring in the fourth and fifth decades of life, respectively.

**surveillance**

Patients at high risk for HCC should be considered for, and offered to be entered into surveillance programmes. These include all cirrhotic HBV carriers; non-cirrhotic patients with high HBV DNA concentration; patients with HCV-related or alcoholic cirrhosis, as well as patients with several rare disorders. Surveillance should be performed using ultrasonography at 6- to 12-month intervals, associated or not with α-fetoprotein (AFP) determination, in order to detect early HCC amenable to surgical treatment with curative intent [II, B]. Despite correct surveillance, there are, however, still no data confirming that these advantages in detection of earlier lesions produce an improvement in long-term survival, and cirrhotic patients Child–Pugh B and C may have rather limited options for curative treatment.

**diagnosis**

Tumors are multifocal in the liver in 75% of cases at diagnosis. Diagnosis is usually made by history, physical examination, imaging (ultrasound, MRI or CT scan showing a liver mass consistent with HCC) and optionally elevated serum AFP (>400 ng/ml), because AFP is elevated in only 50%–75% of cases. A suspicious lesion on the sonogram generally requires additional imaging studies to confirm the stage of the tumour and sensitivity for detection of small nodules may be low. The addition of arterial phase imaging to conventional CT scanning increases the number of tumour nodules detected, but in nodular cirrhotic livers the sensitivity to detect HCC is low. The overall sensitivity of MRI is similar to that of triphasic CT scan, but in patients with nodular cirrhotic livers MRI has better sensitivity and specificity. Confirmation of diagnosis is made by fine needle aspiration or biopsy. Elevation of AFP >400 ng/ml can be used instead of fine needle cytology for diagnosis of HCC in patients with liver cirrhosis and a focal hypervasular liver lesion (>2 cm) in at least one imaging technique. Patients with potentially resectable liver mass and AFP >400 ng/ml should undergo surgery without preoperative fine needle aspiration cytology or biopsy. Any deterioration in liver function in a patient with known liver cirrhosis of any aetiology should raise a suspicion of HCC.

As an increasing number of cirrhotic patients and/or HBV/ HCV carriers are entered into surveillance programmes, it is most likely that in a substantial number of patients, classical echosonography will be the initial imaging technique raising a suspicion of HCC. Afterwards the size of lesions and the presence or not of cirrhosis will influence the sequence of tests used to diagnose HCC. Suspect nodules <1 cm should be...
followed with ultrasound at intervals of 3–6 months; nodules between 1 and 2 cm in a cirrhotic liver should be investigated with at least two dynamic studies (triphasic CT scan, ultrasound or MRI with contrast). If two techniques show a typical appearance of HCC, the nodule should be interpreted as such; if that is not the case, the lesion should be either biopsied whenever possible or extirpated at the discretion of the physician. Nodules >2 cm with a typical feature of HCC on a dynamic imaging technique, as well as any nodule associated with AFP concentration >400 ng/ml or rising AFP on sequential determinations need not be biopsied but should be considered as proven HCC, and appropriate available treatment modalities should be started.

**staging and risk assessment**

Staging should include X-ray of chest (alternatively CT scan) and CT scan (alternatively MRI) of the abdomen. Imaging studies for eventual other tumour localizations should be performed as needed according to the clinical context. CT scan of the chest and bone scintigraphy have to be performed in transplant candidates. Tumors should be staged according to AJCC staging criteria/TNM system, although it appears to be of less predictory value than the CLIP (Cancer of the Liver Italian Program) and the BCLC (Barcelona Clinic Liver Cancer) staging. In fact, in most patients with HCC we are dealing with two diseases, each one of them independently determining our treatment possibilities and final patient outcome: the cancer itself and the underlying liver disease. Thus, an optimal staging system targeting treatment modalities should include grading of both. Transplant candidates must be evaluated according to the current listing criteria.

The fibrolamellar variant is not associated with cirrhosis of any aetiology, is not associated with increased AFP serum concentrations and, if resectable, has a more favourable prognosis.

For patients being considered for liver transplantation, MELD (Model for End-stage Liver Disease) score is mandatory. Child–Pugh grade A patients and selected favourable grade B ones should be evaluated for specific treatment options. For the fibrolamellar variant, local treatment modalities are the only ones to be considered, as there is no documented chemotherapy regimen or biological agent that has shown any activity.

**treatment plan**

The treatment of every patient with HCC should always be discussed and planned by a multidisciplinary team. The treatment plan should be based on the presence or absence of liver cirrhosis, extent of disease, growth pattern of tumour, hepatic functional reserve and patient’s performance status. The applicable treatment possibilities include surgical (liver resection, liver transplantation), ablative (transarterial chemoembolization, radiofrequency ablation) and medical (sorafenib) modalities. Due to the MELD-score-oriented allocation policy during recent years, selected Child C patients with HCC within the Milan criteria may be discussed for liver transplantation. Child–Pugh grade C patients should be offered only supportive care if their tumour exceeds current listing criteria.

**surgical modalities**

**liver resection**

Liver resection is the first-line option for patients with localized resectable tumours in the non-cirrhotic liver, or in selected patients with Child–Pugh A liver cirrhosis. A 3-year survival of 54% is reported in patients with HCC in the non-cirrhotic liver after performance of R0 resections, i.e. resections with tumour-free surgical margins. At the moment there are no recommendations concerning eventual adjuvant treatment after R1 resection. In the case of localized intrahepatic tumour recurrence after liver resection, re-evaluation for surgery has to be considered. For relapses not amenable to surgery, ablative treatments alone, or sorafenib may be applied. For diffuse intrahepatic tumour recurrence after liver resection in the non-cirrhotic liver, the possibility of liver transplantation may be discussed in selected cases as an extended indication, but only in specialized centres.

**liver transplantation**

Liver transplantation offers the best long-term effective treatment for patients with HCC in cirrhosis. Patients that fulfill Milan criteria (single tumour ≤5 cm; two or three tumours, none >3 cm; no vascular invasion), or the expanded University of California San Francisco criteria (UCSF criteria: single tumour ≤6.5 cm; two or three tumours, none >4.5 cm; or total tumour diameter ≤8 cm; no vascular invasion) may have a 3-year survival of up to 88%. The expansion of the tumour-specific criteria for transplantation is a topic of discussion and disputation in hepatological and transplant congresses. Recently, the ‘up-to seven criteria’ (in the absence of microvascular invasion, seven is the result of the sum in cm and number of tumours for any given HCC) were proposed in an effort to include additional HCC patients as transplant candidates; however, the radiological recognition of microvascular invasion is a topic of debate. Several studies suggested poor post-transplant results for HCC patients with elevated AFP (>400 ng/ml), age >60 years and MELD score >20. Post-transplant treatment with mTOR inhibitors (sirolimus, everolimus) in order to reduce the risk of recurrence are currently evaluated in prospective studies. In the case of localized intrahepatic recurrence, all modalities from liver resection, re-transplantation up to medical treatment must be evaluated. In the case of extrahepatic recurrence, sorafenib is the treatment of choice for selected patients.

At present, according to the accepted transplant policy, liver transplantation can be performed for patients with HCC fulfilling Milan or UCSF criteria. Liver transplantation for patients with HCC exceeding these criteria may be discussed in large-volume centres, having the possibility either to perform split liver transplants or to accept marginal grafts, or to perform live donor liver transplantation. Such transplant indications have to be evaluated individually by the corresponding ethic committees and transplant boards.
CLIP scores range from 0 to 6 (CLIP 0 function.

Risk assessment is based on Pugh’s modification of Child’s grading of liver physical status.

Specifically, BCLC staging system (which includes the Okuda staging) may improve prediction of the ultimate prognosis of HCC patients.

Staging systems such as CLIP or BCLC that include staging of liver cirrhosis may improve prediction of the ultimate prognosis of HCC patients. Specifically, BCLC staging system (which includes the Okuda staging) appears more useful than the TNM for planning future patient management since it takes into account tumour stage, liver function and physical status.

**Table 2. CLIP classification**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Child–Pugh</td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>0</td>
</tr>
<tr>
<td>B</td>
<td>1</td>
</tr>
<tr>
<td>C</td>
<td>2</td>
</tr>
<tr>
<td>Tumour morphology</td>
<td></td>
</tr>
<tr>
<td>Uninodular and extension &lt;50% of liver</td>
<td>0</td>
</tr>
<tr>
<td>Multinodular and extension &lt;50% of liver</td>
<td>1</td>
</tr>
<tr>
<td>Massive or extension ≥50% of liver</td>
<td>2</td>
</tr>
<tr>
<td>Alpha fetoprotein</td>
<td></td>
</tr>
<tr>
<td>&lt;400 ng/ml</td>
<td>0</td>
</tr>
<tr>
<td>&gt;400 ng/ml</td>
<td>1</td>
</tr>
<tr>
<td>Macrovascular invasion</td>
<td>0</td>
</tr>
<tr>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1</td>
</tr>
</tbody>
</table>

Risk assessment is based on Pugh’s modification of Child’s grading of liver function.

CLIP scores range from 0 to 6 (CLIP 0 = 0 points, CLIP 1 = 1 point … etc.).

**ablative modalities**

**Transarterial chemoembolization**

Transarterial chemoembolization (TACE) represents an accepted treatment of HCC in the setting of cirrhosis, either as a palliative technique per se, or as a ‘bridging’ modality before liver transplantation. In the latter case, the goal is to downstage patients whose tumours exceed accepted transplant listing criteria, or to achieve local tumour control for patients who meet the tumour listing criteria while on the waiting list for liver transplantation (if waiting list exceeds 6 months). The TACE principle is intra-arterial injection of cytotoxic drug combinations like doxorubicin and/or cisplatin and/or mitomycin into the hepatic artery, followed by lipiodol injection, gelfoam for vessel occlusion and degradable microspheres [II, A].

An aggressive ablation therapy in association with a short transplant waiting time has the potential to optimize the curative intent of liver transplantation in selected cirrhotic patients. According to the local extension of the disease and the hepatic functional reserve, TACE may be performed as a ‘complete’ one a selective one, or a super-selective one, with application through a microcatheter. Contraindications to TACE include Child–Pugh C liver cirrhosis, presence of multifocal bilobar tumour spread, presence of extrhepatic metastases, portal vein thrombosis or arterio-portal fistula.

**Radiofrequency ablation**

Radiofrequency ablation (RFA) represents a widely applied method to treat HCC in a palliative intent, or as a ‘bridging’ to liver transplantation. It may be performed under ultrasonography or CT guidance, or during laparoscopic and open surgical procedures. It has some more limitations in comparison with TACE, such as the number of the nodules that may be treated (up to three in most centres) or the maximal tumour diameter of the nodules (up to 5 cm). Effective treatment has been achieved, when a 100% tumour necrosis is present. However, it is unlikely to reach this goal with tumours exceeding the above mentioned diameter or number of tumour nodules.

**Other ablative procedures**

Percutaneous ethanol injection (PEI), cryotherapy, microwave coagulation therapy are alternative modalities to RFA, which have not met such a wide application as RFA. PEI is indicated in patients with fewer than three or four tumour nodules, maximum 5 cm in size [III, B]. The efficacy of PEI is clearly inferior to RFA in tumours >5 cm [II, B].

**Yttrium-90 microsphere radioembolization**

Yttrium-90 (Y90) microsphere radioembolization is a recently FDA-approved, non-surgical procedure used to treat inoperable
HCC. This innovative procedure delivers targeted, internal radiation therapy directly to the tumour. There are some promising reported results for this technique either as a 'bridging' option before other treatment modalities (partial hepatectomy, liver transplantation) or as a main therapy for patients with diffuse intrahepatic tumour spread. Once the catheter is properly placed in the hepatic artery, microspheres, which contain the radioactive Y90, are released into the hepatic bloodstream. These microspheres lodge in the smaller blood vessels that feed the tumour. In addition to preventing blood flow to the tumour, the microspheres emit radiation that helps to destroy the cancerous cells. Due to the targeted nature of this approach, it can deliver a much more potent dose of radiation than conventional radiation therapy. The radioactivity of Y90 continually decreases over a 2-week period, at which time the radioactivity is essentially gone. Number and size of tumours does not need to be determined for treatment to be effective. Treatment with Y90 microspheres has the advantage of being able to treat all intrahepatic HCC lesions, including otherwise undetected tumours. It may also be the alternative to TACE in selected patients with contraindications for TACE. Extrahepatic metastases are also a contraindication to Y90 microsphere radioembolization.

**radiotherapeutical modalities**

Management of patients with invasion of the portal vein or inferior vena cava invasion is debatable. Investigational but clinically applicable options for selected patients (large solitary tumour with a few satellites and a sufficient amount of healthy liver to be spared) include:

- Radioembolization with Y90 microspheres as previously described for patients with branch or lobar portal vein thrombosis (PVT).
- Three-dimensional conformal radiotherapy (3D-CRT) 30–60 Gy for patients with no or Child–Pugh grade A cirrhosis and tumour invasion of the inferior vena cava, or patients with PVT of the main branch.

- Portal vein stenting followed by 3D-CRT and TACE for patients with main portal vein tumour thrombosis.

**medical modalities**

Until recently there has been no standard medical therapy for advanced HCC. The positive results of a Phase III study called the Sorafenib Hepatocarcinoma Assessment Randomized Protocol (SHARP), which assessed the use of sorafenib in patients with unresectable HCC introduced this medication as the first promising one in the systemic treatment of HCC. Sorafenib induced in a previous Phase II study response in 8% and disease control in 41% of patients. In two Phase III studies with patients with Child–Pugh grade A liver disease, it extended survival for 2.8 months as compared with placebo, and is more and more widely accepted as a standard first-line option for systemic treatment [I, A].

Systemic chemotherapy should not be included in standards of care but may be discussed with and offered to selected candidates for systemic treatment if no other options are locally available. Systemic chemotherapy containing anthracyclines (if bilirubin normal and hepatic reserve adequate) was reported to have a prospect of a 10% response rate but no survival benefit. Cisplatin-based combinations were reported to improve response rate but again with no survival benefit as compared with supportive care alone [III, C]. In the PIAF regimen

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**Table 4. Definition of the BCLC staging for HCC**

<table>
<thead>
<tr>
<th>Stage</th>
<th>PST</th>
<th>Tumor status</th>
<th>Liver function status</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Tumor stage</td>
<td>Okuda stage</td>
</tr>
<tr>
<td>A</td>
<td>0</td>
<td>Single, &lt;5 cm</td>
<td>I</td>
</tr>
<tr>
<td></td>
<td>A2</td>
<td>Single, &lt;5 cm</td>
<td>I</td>
</tr>
<tr>
<td></td>
<td>A3</td>
<td>Single, &lt;5 cm</td>
<td>I</td>
</tr>
<tr>
<td>A4</td>
<td>0</td>
<td>3 tumours &lt;5 cm</td>
<td>I</td>
</tr>
<tr>
<td>Stage B: intermediate HCC</td>
<td>0</td>
<td>Large multinodular</td>
<td>I–II</td>
</tr>
<tr>
<td>Stage C: advanced HCC</td>
<td>1–2</td>
<td>Vascular invasion or</td>
<td>I–II</td>
</tr>
<tr>
<td></td>
<td></td>
<td>extrahepatic spreada</td>
<td></td>
</tr>
<tr>
<td>Stage D: end-stage HCC</td>
<td>3–4</td>
<td>Any</td>
<td>IIIb</td>
</tr>
</tbody>
</table>

Stages A and B: all criteria should be fulfilled.
Stage C: at least one criterion; *PST 1–2 or vascular invasion/extrahepatic spread.
Stage D: at least one criterion; *PST 3–4 or Okuda stage III/Child–Pugh C.

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**Table 5. Definition of the Okuda staging system for HCC**

<table>
<thead>
<tr>
<th>Points</th>
<th>0</th>
<th>1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumour size</td>
<td>&lt;50% of liver</td>
<td>&gt;50% of liver</td>
</tr>
<tr>
<td>Ascites</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Albumin (g/dl)</td>
<td>≥3</td>
<td>&lt;3</td>
</tr>
<tr>
<td>Bilirubin (mg/dl)</td>
<td>&lt;3</td>
<td>3</td>
</tr>
</tbody>
</table>

Okuda stage I, 0 points; Okuda stage II, 1 or 2 points; Okuda stage III, 3 or 4 points.
considered. Best supportive care is the only option for patients with HCC that is outside the current listing criteria for transplantation, such as active alcohol abuse in the setting of hepatitis and/or liver cirrhosis and viral replicative status. For other patients, follow-up aims to prevent and/or treat hepatic decompensation.

Transplanted patients should be followed only in specialized transplant centres. Post transplantation treatment includes corticosteroids, calcineurin inhibitors (ciclosporin or tacrolimus), mycophenolate mofetil or mTOR inhibitors (sirolimus, everolimus). Follow-ups should be scheduled once monthly up to 6 months, then once every 3 months up to 1 year, than twice a year up to 2 years and once a year every year thereafter. Imaging studies should be performed as needed. The follow-up is aimed at drug dosage adjustment, early diagnosis of eventual immunosuppression-related infection, early detection of rejection or transplant dysfunction, and later also at detection of immunosuppression-related neoplasia. Antiviral therapy should be continued if previously started.

**note**

Levels of evidence [I–V] and grades of recommendation [A–D] as used by the American Society of Clinical Oncology are given in square brackets. Statements without grading were considered justified standard clinical practice by the experts and the ESMO faculty.
literature


