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REVIEW

# Hepatocellular carcinoma: Dutch guideline for surveillance, diagnosis and therapy

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## ABSTRACT

Hepatocellular carcinoma (HCC) is rare in the Netherlands, even though the incidence has increased quite sharply in recent years. Standard treatment options consist of surgery, orthotopic liver transplantation, radiofrequency ablation, transarterial chemoembolisation (TACE) and systemic therapy with sorafenib. The consensus-based Dutch HCC guideline, established in 2013, serves to guide surveillance, diagnosis and treatment options:

- Surveillance should be performed by ultrasound at six-month intervals in well-defined cirrhotic patients and in selected high-risk hepatitis B carriers;
- A nodule > 1 cm in cirrhotic patients with arterial hypervascularity and venous or delayed phase washout at four-phase CT or MRI scan establishes the diagnosis of HCC;
- In patients with HCC without underlying cirrhosis, resection should be considered regardless of tumour size;
- In cirrhotic HCC patients, tumour stage, severity of underlying cirrhosis, and performance status determine treatment options. The algorithm of the Barcelona Clinic Liver Cancer (BCLC) staging system should be followed;
- Patients with Child-Pugh A-B cirrhosis (CP < 8 points) and performance status 0-2 are candidates for any active treatment other than transplantation;
- In early stage HCC (BCLC stage 0 or A, compensated cirrhosis without portal hypertension) surgical resection, liver transplantation, or radiofrequency ablation should be considered;
- In intermediate stage HCC (BCLC stage B) TACE and/or radiofrequency ablation should be considered;
- In advanced stage HCC (BCLC stage C) sorafenib should be considered.

Conclusion: The Dutch HCC guideline offers advice for surveillance, diagnosis and treatment of HCC.

## KEYWORDS

Diagnosis, hepatocellular carcinoma (HCC), surveillance, treatment

## INTRODUCTION

Primary liver cancer is the sixth most common cancer in the world and the third cause of cancer-related death.[1] Hepatocellular carcinoma (HCC) represents more than 90% of primary liver cancers. Liver transplantation and resection are curative treatment options in HCC. In practice, only a minority of patients with HCC fulfil the criteria for potential cure.

Patients with HCC within the 'Milan criteria' (one nodule < 5 cm or up to three nodules each < 3 cm in diameter without macroscopic vascular invasion or extrahepatic disease) can be considered for liver transplantation. Resection of HCC is not possible in case of decompensated cirrhosis or portal hypertension.

Several local treatment options for unresectable HCC have been introduced in recent years. With radiofrequency ablation, a thin probe is inserted (generally percutaneously) under ultrasound or computed tomography (CT) guidance

in the tumour, and local ablation is obtained by heating to 60-100 °C.[2] With transarterial chemoembolisation (TACE), a catheter is placed in the feeding artery of the tumour. With radioembolisation or selective internal radiotherapy (SIRT), a catheter is placed in the artery supplying the tumour.[3,4] Treatment is pursued through local application of chemotherapy or radiotherapy, and in case of TACE combined with arterial embolisation. A cure is rarely obtained with TACE or SIRT, and currently SIRT is still considered to be an experimental treatment. In advanced or metastatic HCC, systemic therapy with the multi-tyrosine kinase inhibitor sorafenib leads to improvement in overall survival in selected patients.[5,6]

In 2011, a national committee with representatives of nurses and relevant medical specialists was installed in order to define a Dutch HCC guideline for surveillance, diagnosis and treatment of HCC. This committee was supported by the Comprehensive Cancer Centre of the Netherlands.

The Dutch HCC guideline has been approved by all relevant Dutch scientific associations and was published in 2013.[7,8] In this article we summarise the most important recommendations from this guideline.

## EPIDEMIOLOGY

Incidence rates of HCC are highest in East Asia and Sub-Saharan Africa, where approximately 85% of all cases occur. Endemic risk factors such as chronic hepatitis B virus infection and aflatoxin B1 in the diet explain the high incidence.[1,9] In the Western world, hepatitis C, non-alcoholic steatohepatitis and alcohol are the predominant risk factors.[10] Coexisting metabolic syndrome can further increase HCC risk in patients with underlying liver disease.[11] Smoking is a factor leading to increased HCC risk, whereas the use of cholesterol synthesis inhibitors, oral antidiabetic agents and coffee consumption are associated with decreased HCC risk.[12-16]

Between 1989-2009, HCC was diagnosed in 5143 patients in the Netherlands. Potential curative treatment (liver resection, liver transplantation, radiofrequency ablation) was offered to 9% of patients in the period 1989-1994 and 23% in the period 2005-2009, whereas palliative treatment (sorafenib, TACE, radiotherapy) was offered to 6% of patients in the period 1989-1994 and 11% in the period 2005-2009. The percentage of patients to whom only supportive care could be offered decreased from 85% in the period 1989-1994 to 66% in the period 2005-2009. Between 1989-2009, one-year and five-year HCC survival rates increased from 20 to 37% and from 5 to 14%, respectively.[17]

## SURVEILLANCE

Despite the introduction of new treatment modalities, survival in patients with advanced HCC remains poor. Thus preventive strategies are urgently needed to decrease the incidence of HCC. Primary prevention of HCC can be achieved by hepatitis B vaccination, and effective antiviral treatment of chronic viral hepatitis is associated with decreased HCC risk in these patients.[18-21] In patients at increased risk of developing HCC due to the presence of chronic liver disease, such as cirrhosis, surveillance by means of ultrasound can detect HCC at an earlier stage.[22] However, surveillance remains controversial because of limited evidence for its efficiency and the potential risk of side effects (due to unnecessary invasive procedures).[23,24] Even though the majority of HCC occurs in patients with underlying cirrhosis, about one out of three cases of HCC in the Netherlands occurs in patients without cirrhosis, hampering the efficacy of screening programs which are only pursued in patients with known underlying risk factors.[25] Ultrasound has been found to have a sensitivity of 63% to detect HCC within the 'Milan criteria'. Sensitivity is 70% in case of a six-month interval and 50% with a 6-12 month interval.[24]

According to the Dutch HCC guideline, surveillance should be offered to patients with cirrhosis due to chronic hepatitis B or C, haemochromatosis, alcohol or primary biliary cirrhosis, as well as to a high-risk hepatitis B virus carriers (*table 1*).[7] In patients with cirrhosis due to non-alcoholic steatohepatitis, autoimmune hepatitis, alpha1-antitrypsin deficiency and Wilson's disease, there is currently no

**Table 1.** *Recommendations for surveillance. Ultrasound with six-month intervals should only be performed in patients with strongly increased risk of HCC*[26]

| |
|---|
| **Patients with chronic hepatitis B.** |
| All patients with chronic hepatitis B and cirrhosis. |
| The following groups of patients with chronic hepatitis B without cirrhosis: |
| • Males from East Asia > 40 years old |
| • Females from East Asia > 50 years old |
| • Patients from sub-Sahara Africa > 20 years old |
| • Patients with a family history of HCC |
| |
| **Non-hepatitis B cirrhosis** |
| • Hepatitis C |
| • Alcoholic cirrhosis |
| • Haemochromatosis |
| • Primary biliary cirrhosis |

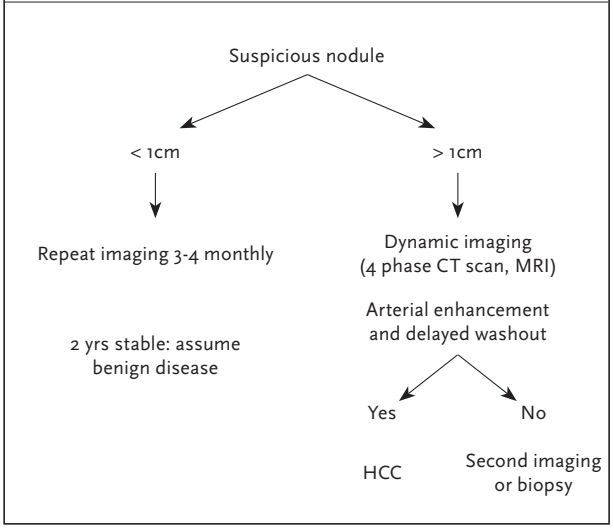
evidence to support surveillance. Moreover, in patients with cirrhosis due to non-alcoholic steatohepatitis, ultrasound is often unreliable due to excessive body weight. There are no data supporting surveillance with CT scan or magnetic resonance imaging (MRI). Surveillance through serial measurements of alpha-fetoprotein is not recommended.

## DIAGNOSIS

If a nodule is detected by ultrasound in a high-risk patient with cirrhosis, radiological investigation by four-phase CT scan (with unenhanced, arterial, venous and delayed phases) and/or dynamic MRI scan is indicated to establish the diagnosis of HCC (*figure 1*). The combination of arterial hypervascularity with venous or delayed phase wash-out is pathognomonic for HCC. Varying results for the sensitivity and specificity of three-phase CT scan (sensitivity 50-87%, specificity 53-87%) and MRI scan (sensitivity 34-100%, specificity 62-100%) have been published.[7] Diagnostic accuracy has improved in the past decade as a result of an improvement in technology. In general, sensitivity and specificity will increase with increasing tumour size, whereas the positive and negative predictive value of a diagnostic procedure will strongly depend on the size of the lesion and the *a priori* HCC incidence in the investigated population. If diagnostic uncertainty remains, one may choose to monitor the lesion at 3-4 month intervals to detect growth.

Despite encouraging preliminary results, contrast-enhanced ultrasound is not recommended as a standard diagnostic due to limited experience and data.[7] PET/CT scan is also not recommended as a standard diagnostic imaging test.

**Figure 1.** *Diagnostic algorithm in case of a suspicious nodule in a patient with increased a priori risk of HCC*




If the diagnosis of HCC cannot be established by means of adequate radiodiagnostic procedures, a tumour biopsy may be considered. It is obvious that adequate tissue sampling and subsequent pathological assessment and reporting are mandatory under these circumstances, and thus it is recommended to perform these procedures only in specialised centres. According to a recent meta-analysis, needle tract seeding occurs in 2.7%, without any effect on patient survival.[27]

The diagnostic protocol is summarised in *figure 1*. In the Dutch HCC guideline, quality standards are given for CT scan, MRI scan, pathology assessment and reporting of results. Recommendations for diagnosis can be summarised as follows:

- Dynamic MRI scan or four-phase CT scan are advised for establishing the diagnosis of HCC;
- In patients with an increased *a priori* risk of HCC, a nodule > 1 cm in diameter with arterial hypervascularity and venous or delayed phase wash-out establishes the diagnosis. If results are inconclusive, one may choose radiological follow-up at 3-4 month intervals or (in expert centres) taking a biopsy of the nodule;
- In case of a nodule < 1 cm in diameter, radiological follow-up at 3-4 month intervals is recommended.

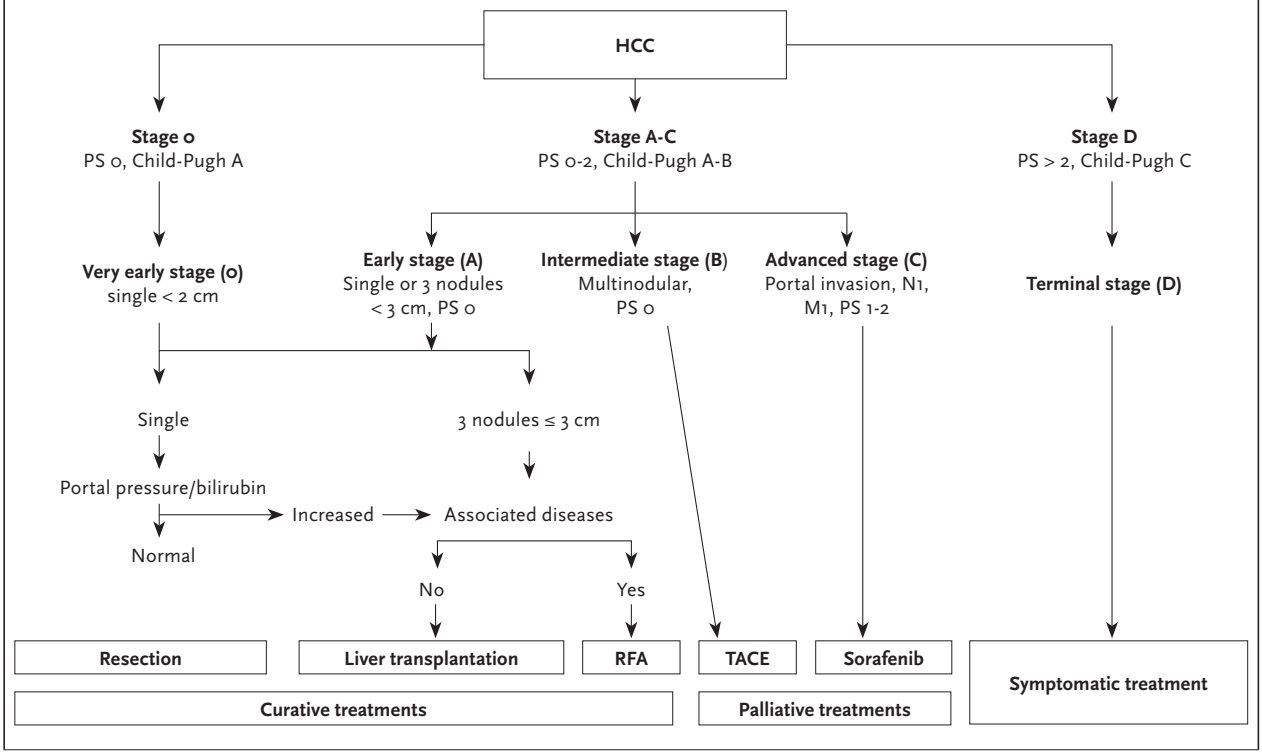
## TREATMENT

In Western countries, the presence of a resectable solitary HCC nodule in a non-cirrhotic liver occurs in approximately 30% of all HCC cases. These patients can usually be treated with curative intent (generally resection), regardless of tumour size. In patients with a potentially resectable HCC lesion with underlying cirrhosis, however, not only tumour size, but also the severity of underlying liver disease and performance status must be taken into consideration. The Barcelona Clinic Liver Cancer (BCLC) staging system is the algorithm of choice to determine therapeutic options for patients with HCC and underlying cirrhosis (*figure 2*).[28] This validated staging system takes into account such relevant parameters as liver functionality (often as a consequence of underlying liver cirrhosis), tumour burden, clinical performance and divides patients into very early/early, intermediate, advanced, and end-stage. In general, only patients with Child-Pugh A-B cirrhosis (preferably CP < 8 points) and performance status 0-2 are candidates for any active treatment other than liver transplantation.

### (Very) early stage (stage 0 or A, within 'Milan criteria')

Resection, transplantation and radiofrequency ablation can offer a cure to these patients.[29-33] Resection should only be performed in centres of expertise in patients with

**Figure 2.** *Treatment options for patients with early, intermediate, advanced or terminal stage HCC depend on BCLC (Barcelona Clinic for Liver Cancer) criteria, incorporating tumour stage, performance status and severity of underlying liver disease*




compensated (Child-Pugh A) cirrhosis in the absence of portal hypertension. For indication and selection for liver transplantation, we refer to: http://www.mdl.nl/uploads/240/846/Levertransplantatie_Protocol_indicatiestelling_en_selectie_maart_938 2011.pdf. The Dutch HCC guideline advises radiofrequency ablation in patients with, at most, moderately compromised liver function (CP class < 8) and with HCC within the 'Milan criteria' if liver transplantation or resection are not possible. It should be noted that radiofrequency ablation can also be performed as 'bridge to transplantation', considering the long waiting times for transplantation in the Netherlands. Also, based upon available literature, radiofrequency ablation is generally preferred over percutaneous ethanol injection, laser-induced thermotherapy or microwave coagulation.[7]

**Intermediate stage (BCLC stage B: outside 'Milan criteria', but no macrovascular invasion or extrahepatic disease: median survival without therapy 15 months)**

Several systematic reviews (including randomised controlled studies) indicate increased survival with TACE when compared with best supportive care.[3,34] However, a recent Cochrane review did not show survival benefit for TACE.[35] This Cochrane review included some studies with unusual patient characteristics and/or relatively short follow-up.

According to the Dutch HCC guideline, radiofrequency ablation can be considered in the intermediate stage with up to three tumour nodules and maximal diameter < 5 cm, provided the Child-Pugh score is less than 8. Considering the limited data available, the Dutch HCC guideline still advises TACE for intermediate stage HCC, especially in case of tumour diameter exceeding 5 cm, while acknowledging that this advice remains controversial. Also, in selected cases, initial TACE may enable subsequent radiofrequency ablation, resection or even liver transplantation by reducing tumour size. Although TACE with drug-eluting beads is more expensive than conventional TACE, and without survival benefit, the Dutch HCC guideline advises drug-eluting beads because of the lower risk of side effects such as liver toxicity and doxorubicin-related systemic side-effects.

**Advanced stage HCC (BCLC stage C: invasion portal vein and/or extrahepatic disease, Child-Pugh A-B, performance status maximal 2: median survival without treatment 6 months)**

Two randomised controlled studies have shown increased overall survival for sorafenib compared with best supportive care in patients with advanced HCC.[5,6,36] Based upon these data, the Dutch HCC guideline states that sorafenib should be considered for patients with

**Table 2.** *Child-Pugh classification for chronic liver disease*

| Parameter | 1 point | 2 points | 3 points |
|---|---|---|---|
| Serum total bilirubin (µmol/l) | < 34 | 34-50 | > 50 |
| Serum albumin (g/l) | > 35 | 28-35 | < 28 |
| INR | < 1.7 | 1.7-2.3 | > 2.3 |
| Ascites | none | Mild | Moderate to severe |
| Hepatic encephalopathy | none | Grade 1-2 (or suppressed with medication) | Grade 3-4 (or refractory) |

**Table 3.** *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 |
| 5 | Dead |

compensated (Child-Pugh A) cirrhosis and advanced stage disease with performance status of 0-2. Patients with Child-Pugh B cirrhosis should preferably be treated in clinical trials based upon limited available data in this group. In addition, sorafenib can be considered for patients with compensated cirrhosis and intermediate stage disease, in case of progressive disease after loco-regional therapy (TACE, radiofrequency ablation) or if such locoregional therapy is not possible for technical or medical reasons.[37]

**Terminal stage (BCLC stage D: Child-Pugh stage C, performance state > 2: median survival < 3 months)**
For patients with terminal stage disease, the only option is best supportive care. These patients should not be treated with any active tumour-directed therapy.

## INNOVATIVE TREATMENT OPTIONS

Promising results have been reported in uncontrolled studies for such treatment options as stereotactic radiotherapy, selective internal radiotherapy or radioembolisation with Yttrium-90, microwave coagulation therapy and laser-induced thermotherapy. The Dutch HCC guideline advises that these innovative treatments should only be applied in clinical trials.

## CONCLUSION

The Dutch HCC guideline offers advice for surveillance, diagnosis and treatment of HCC. In addition, the Dutch Working Party on Hepatocellular Carcinoma has initiated and facilitated multidisciplinary communication, concept and design for a national registry, and meanwhile various preclinical and clinical study initiatives are pursued under its umbrella.

## DISCLOSURES

All authors declared no conflict of interest, commercial affiliations, consultations, stock or equity interests.

Additional members of the Dutch working party hepatocellular carcinoma:
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