BASL guidelines for the surveillance, diagnosis and treatment of hepatocellular carcinoma

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1. Introduction

Hepatocellular carcinoma (HCC) is a primary tumour of the liver. Its behaviour is rather peculiar with prognosis made out not only by the tumoural disease but also by the severity of the underlying liver disease. Worldwide it is a major problem. In the West, however, the prevalence is lower than in developing countries. However due to a rise in HCV induced liver cirrhosis, HCC becomes more prevalent in Belgium. In the HepCar registry (a Belgian registry where on a voluntary basis, patients with HCC are reported), 70 patients (51 male / 19 female) were reported between January 2003 and September 2003. Median age was 62 years ± 12. Underlying liver disease was HCV in 29 patients, HBV in 14 patients, alcoholic liver disease in 16 patients and miscellaneous in 12 patients. Diagnosis was made by surveillance in 27 patients. There was a clear tendency for incidental diagnosis in patients with alcoholic liver disease.

Due to this changing pattern of HCC in Belgium, a BASL working group was founded to discuss and report on guidelines in epidemiology, screening, diagnosis and treatment of HCC. These guidelines are a result of a discussion between the different members of the working group reflecting data published in literature and taking into account the specific Belgian situation. Expert opinion should be based on scientific studies and on evidence coming from well performed clinical trials. Recommendations contained herein are based on the best available data or, when these are lacking, the collective experience of the members of the writing committee. Agreement or consensus was not always reached.

2. Epidemiology

Primary liver cancer is obviously an important public health problem in Far East and Sub-Saharan Africa where it accounts for one of the most frequent cancers due to endemic hepatitis B infection. In these regions, the mortality by HCC is about 100 per 100 000 habitants (1,2).

Conversely, HCC is a hitherto relatively rare cancer in western countries. In Belgium, statistics from de National Cancer registry for the 1993-1995 period showed that the annual incidence of cancer classified as ICD 155 (International Classification of Disease – 7th revision) including primary liver, gallbladder and bile duct cancers was 4.9/100 000 in men and 5.2/100 000 in women. According to these statistics, the annual incidence of HCC is in a range of 2-3 per 100 000 habitants making of Belgium a low-incidence area for HCC. At first glance, it seems therefore not justified to launch large and costly programs of surveillance for HCC in Belgium. However it is likely that the increase in the incidence of HCC follows the epidemic of hepatitis C virus infection that occurred in late sixties and early seventies. In the United States, the incidence of histologically proven hepatocellular carcinoma increased from 1.4 per 100 000 for the period 1976-1980 to 2.4 per 100 000 for the period 1991-1995 (3). Epidemiological analyses have shown that hepatitis C virus infection accounted for most of this increase, while the rates of primary liver cancer associated with alcoholic cirrhosis and hepatitis B infection remained stable (4).

3. Prevention of hepatocellular carcinoma (HCC)

3.1. *Primary prevention*

The prevention of the development of liver diseases and of their progression to cirrhosis is the most effective way to prevent HCC :

- Hepatitis B : the main cause of HCC in the world, can effectively be prevented by vaccination. Vaccination in children in Taiwan has led to a drastic decrease in the incidence of HCC (5,6).

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- Hepatitis C : Unfortunately, up to now there is no vaccine against hepatitis C. The only effective method to prevent its transmission is the avoidance of contamination with infective blood products.
- Prevention and early detection of alcohol abuse.
- Screening and treatment of haemochromatosis.

3.2. *Prevention of HCC in patients with previously acquired risk*

Chronic viral carriage is one of the main risk factors for the development of HCC. Effective antiviral treatments have been developed in recent years and this has changed the management of viral infection.

3.2.1. Treatment in HBV patients and HCC prevention

3.2.1.1. Treatment with interferon

3.2.1.1.1. Noncirrhotics

In patients with chronic hepatitis B, clearance of the HBeAg after treatment with interferon-alpha is associated with improved clinical outcome in terms of survival and development of complications of cirrhosis (7). Another study confirmed these results and showed a reduction of HCC in the responders (8). As most of these patients were noncirrhotics at entry of the study, the prophylactic effect of interferon on development of HCC can be explained by prevention of cirrhosis development.

3.2.1.1.2. Cirrhotics

Several studies have investigated the effect of interferon treatment on development of HCC in patients with already established cirrhosis. A meta-analysis was performed on these studies (9). Interferon seemingly decreased the rate of HCC in all trials, while significant difference was observed in 2 studies. Virologic response was strongly associated with reduced risk for HCC in some studies, indicating that arrest of viral replication is a critical factor. Subgroup analysis in relation to ethnic origin of patients (European, Oriental) showed no preventive effect of interferon on the development of HCC in the European patients. It should be noted that the studies are very heterogeneous and that none of them were randomised controlled trials, so that the results should be interpreted with caution.

3.2.1.2. Treatment with nucleoside/nucleotide analogues

Up to now, there are no data published in full paper, on the effect of these antivirals on the prevention of HCC in chronic hepatitis B.

3.2.2. Interferon treatment in HCV patients and HCC prevention

3.2.2.1. Noncirrhotics

Pooling of incidence of HCC in noncirrhotic patients with chronic hepatitis C from 3 studies showed a lower incidence in patients with sustained virologic response (SVR) than in nonresponders (10-12).

3.2.2.2. Cirrhotics

Cammà *et al.* (9) performed a meta-analysis of 3 randomised and 11 nonrandomised studies on hepatitis C cirrhosis. In 13 of these studies, interferon reduced the incidence of HCC with a statistical significance in 10 studies. The effect was more beneficial in patients who achieved a sustained biochemical response. The overall result was largely influenced by three Japanese studies. Four European studies failed to document a significant reduction in risk of developing HCC.

There are various explanations for the differences in the result of these studies. First, in Japan, the sustained virological response rate (SVR) to interferon monotherapy is higher than observed in Europe or the US. Second, the incidence of HCC is much higher in Japan. Both factors make it easier to show a preventive effect of therapy. Furthermore, there are important methodological questions. The majority of the studies are retrospective and nonrandomised, introducing a bias in the selection of patients for therapy. Also, different definitions of response (biochemical, virological) are used. The still unanswered question is whether interferon therapy can be beneficial in biochemical responders but virological non responders.

Because of potential biases in the published trials, it is premature to advocate the use of interferon as established therapy in HCV infected patients to prevent HCC. Prospective randomised controlled trials should reproduce the findings in large numbers of patients before a definitive conclusion on the long-term effects of interferon in HCV cirrhosis can be established. It should also be investigated in prospective trials if more performant treatment regimens with peginterferons and combination of (peg)interferon and ribavirin will also favourably influence the incidence of HCC.

<u>Recommendations</u>

- The most effective tool to prevent HCC is avoidance of risk factors such as viral infection. Universal vaccination against hepatitis B virus should be a health priority.
- In patients with chronic hepatitis B or C, interferon treatment in a non cirrhotic stage is protective for HCC development in responders, probably by prevention of cirrhosis development.
- As most studies are not randomised controlled trials, no definitive conclusions on the long-term effect of interferon-alpha in HBV or HCV cirrhosis can be established.
  - For cirrhosis due to hepatitis B, a protective effect of interferon treatment was only demonstrated in Oriental, but not in European patients.
  - For cirrhosis due to hepatitis C, interferon treatment showed to be protective in some studies,

especially Japanese with high incidence of HCC in untreated patients.
– Further prospective studies should be performed in chronic hepatitis B and C. Furthermore, in chronic hepatitis C, the use of the more potent reference treatments namely the combination of peginterferon and ribavirin, should be investigated.

4. Screening and surveillance

Surveillance for HCC in high-risk populations has become a popular clinical practice in western countries. Nevertheless, it has up to now not been fully demonstrated that primary liver cancer ideally fulfils the accepted rules justifying surveillance. According to the World Health Organisation (13,14), surveillance programs should fulfil the following criteria :

1. The disease is recognised as an important public health problem.
2. Populations of high-risk patients can be identified.
3. The clinical stage of the disease is preceded by a period of latency when the disease is detectable.
4. Effective, safe and financially acceptable tools of early detection are available.
5. Curative treatment exists at an early stage resulting in survival improvement.

If it is widely accepted that surveillance for HCC fulfils the first 4 criteria, the last one, however, remains hotly debated.

4.1. *Populations of high-risk patients can be identified*

Risk factors for HCC have been clearly identified : cirrhosis regardless of the aetiology, chronic HBV and HCV infections, aflatoxin exposure, haemochromatosis, hereditary tyrosinaemia. Hepatocarcinoma typically does not occur in the absence of cirrhosis. Cirrhosis is present in more than 80% of the cases in most series of HCC (15) and exceeds 90% in frequently quoted studies aimed at determining the prognosis of HCC (16,17). The annual incidence of HCC in patients with cirrhosis is estimated to be around 3%. In chronic viral hepatitis without cirrhosis, the annual incidence of HCC is less than 1% for chronic hepatitis B (20-23) and about 1.5% for chronic hepatitis C (22,24). Studies suggest that in chronic hepatitis C, HCC develops only at a stage of cirrhosis or extensive fibrosis whereas in chronic hepatitis B, the occurrence of HCC is possible without extensive fibrosis suggesting an oncogenic potential of the virus (18).

Finally, it must be pointed out that the combination of different risk factors has a cumulative impact on the incidence of primary liver cancer : HBV and HCV coinfection in European patients (31), HBV and HCV infections in alcoholic cirrhosis (19). For chronic hepatitis B, familial clustering (25) and positivity for HBe Ag (23) are associated with a greater risk of HCC.

In Belgium, surveillance for HCC addresses almost exclusively patients with cirrhosis.

It is widely accepted that in Belgium, as in other countries from central and northern Europe, the main aetiological factor of cirrhosis and HCC remains excessive alcohol consumption . In a recent cohort of 411 consecutive Belgian patients with cirrhosis, the main aetiologies of cirrhosis were alcohol abuse in 63% and chronic hepatitis C virus infection in 20% (26). The fact that alcohol is the main aetiology of cirrhosis in Belgium is not without consequence for the success of a surveillance program. Indeed, patients with alcoholic cirrhosis are obviously less observant than patients with cirrhosis of viral origin (27). Although alcohol abuse remains the main cause of cirrhosis in Belgium, the role of hepatitis C virus infection in the emergence of HCC clearly becomes more important in recent years. In the same study of 411 Belgian patients with cirrhosis mainly of alcoholic origin (63%), the main risk factor in 57 consecutive cases of HCC was hepatitis C virus infection in 44% followed by alcohol in 33% (26). These results must be compared with the figure observed in a previous Belgian series of HCC where the main risk factor was abusive alcohol consumption in 77% of the cases (28).

4.2. *The clinical stage of the disease is preceded by a period of latency when the disease is already detectable*

Primary liver cancer enters its clinical phase at a size of about 10 cm. From this moment on, the prognosis is dreadful with a median survival less than 4 months (16,29,30). Before reaching the clinical phase, HCC has a relatively slow-growing pattern at least for the so-called encapsulated and expending type that is frequent in European patients (31). The doubling time of small nodules of HCC has been assessed in several studies and ranged between 3 and 6 months placing HCC in the slow-growing group of tumours.

4.3. *Effective, safe and financially acceptable tools of early detection are available*

Serum alfa-foetoprotein (αFP) and liver ultrasonography (US) are the usual tools of the surveillance for primary liver cancer in at-risk patients. It is now admitted that αFP is not an ideal tumour marker for the early detection of small HCC. Indeed, for the detection of a small HCC not exceeding 3 cm in diameter, a slightly elevated level of aFP about 20 ng/ml has a sensitivity in a range 30-60%, a specificity in a range 70-90% and a low positive predictive value of about 20% (32,33). Conversely, a higher value about 200 ng/ml has a better specificity but a low sensitivity in a range 10-25% (32). However, even if αFP is not useful for the diagnosis of small HCC, it remains the most powerful predictive factor of further emergence of HCC and is interesting for determining the periodicity of screening in the surveillance program. An interval screening not exceeding

3 months should be recommended when αFP is slightly elevated (34,35).

Liver US is the most appropriate tool for surveillance of cirrhosis and early detection of small HCC. It is effective in this particular field, it is a non-invasive, non-expensive imaging technique and it is convenient for the patient. Liver US may detect hepatic nodules at a threshold of about 1 cm diameter and, in experienced hands, should detect the vast majority of HCC nodules at a size less than 3 cm in diameter (36). The importance of the quality of the US examinations performed by the same, experienced operator has been pointed out by investigators who reported good results (27,37).

4.4. *Curative treatments exist at an early stage resulting in survival improvement*

Several surveillance studies were disappointing showing a low rate (around 10-20%) of resectability for small HCC identified during surveillance due to poor liver function, co-morbid medical conditions or technical reasons such as a tumour deeply placed or close to vital structures (37,38,39). Moreover, in some of these studies, when a HCC was detected, survival was not different between untreated and surgically treated patients (38,40). Trends in HCC survival in Europe (41) and in US (42) have shown a small improvement comparing the late seventies and early nineties with a 1-year survival improving from 8% to 18% (41) and 14 to 23% (42) respectively, but this could be attributed to the "lead-time bias" i.e. an artificial survival period corresponding to the interval from the point of detection by screening to the usual point of detection in the absence of screening (106).

Nevertheless, a growing body of evidences strongly suggests that surveillance of patients with cirrhosis for the early detection of HCC could be effective in terms of survival prolongation at least in well selected cases. Moreover it seems unlikely that new randomised controlled trials will be put up to solve this issue.

Recommendations

In Belgium, surveillance for HCC addresses almost exclusively patients with cirrhosis regardless of the aetiology, patients with chronic hepatitis C with extensive fibrosis of F3 stage in the METAVIR classification and HbsAg carriers. In these at-risk patients, surveillance should be reserved to those manifesting their willingness to attend the surveillance program and exhibiting a life expectancy of at least 5 years. Alcoholic patients unable to stop drinking and patients with poor liver function (Child's C cirrhosis) – except when transplantation is considered – and severe co-morbid medical conditions should not be included.

- The pivotal tool for surveillance is liver US. αFP is useless for the diagnosis of small HCC but is of great interest for determining the interval between screenings. Ideally, the US should be performed by the same, experienced operator
- The schedule of the surveillance program could be as follows :
  - For patients with compensated cirrhosis, liver US should be performed every 6 months or every 3 months when α-FP is above 20 ng/ml.
  - For patients with chronic hepatitis C and F3 fibrosis, and for patients with chronic hepatitis B, the surveillance interval should be 6 months.
  - For inactive HBs carrier, the surveillance interval should be 12 months or 6 months in case of familial history of HCC.

5. Diagnosis of HCC

Hepatocellular carcinoma (HCC) develops in 80% on a cirrhotic liver, whatever the cause, which is more often hepatitis C (HCV) virus and alcohol in Belgium ; more rarely on HBV or HCV carriers without cirrhosis, and exceptionally on normal liver. Therefore, liver status has to be assessed. If HCC is suspected and no proof of cirrhosis is made by non-invasive investigations, a biopsy of the non-tumoural liver is mandatory.

5.1. *Cirrhosis present :*

a. Characteristic tumour (arterial hypervascularization) of ≥ 2 cm on US or CT or Magnetic Resonance Imaging (MRI) and αFP level above 400 ng/mL : *Diagnosis of HCC* (43)
b. Characteristic tumour (arterial hypervascularization) of ≥ 2 cm, assessed by two concordant imaging techniques (contrast enhanced US and/or CT and/or MRI) : *Diagnosis of HCC* (43)
c. Suspect tumour between 1-2 cm on US : *Probable HCC diagnosis* (44), to be confirmed by raised αFP or CT/MRI and consider option d) in cases of doubt.
d. Other situation : two options are possible :
   - biopsy for diagnosis with a fine needle biopsy technique. In this approach it should be taken into account that a small, but definite risk of seeding exists. This risk could be diminished by the use of a fine needle biopsy (i.e. outer diameter ≤ 0.9 mm or ≥ 19G). However, the rate of false negatives could be higher by the use of this technique where a smaller tissue sample is preserved.
   - Repeat imaging (CT or MRI)/AFP every 3 months : if raised αFP and growing lesion : *Highly Probable HCC diagnosis* (45) .

   However the decision of which option is the best in each individual case, should be discussed in a multidisciplinary approach.

Table 1. — **The Barcelona-Clinic Liver Cancer staging system (54)**

Stage	Performance status	Tumor stage	Liver function
Stage A : early HCC			
A1	0	Single, < 5 cm	No portal HTN and normal bilirubin
A2	0	Single, < 5 cm	Portal HTN and normal bilirubin
A3	0	Single, < 5 cm	Portal HTN and elevated bilirubin
A4	0	3 tumors < 3 cm	Child-Pugh class A-B
Stage B : intermediate HCC	0	Large multinodular	Child-Pugh class A-B
Stage C : advanced HCC	1-2[a]	Vascular invasion or extrahepatic spread[a]	Child-Pugh class A-B
Stage D : end-stage HCC	3-4[b]	Any	Child C[b]

NOTE. Stage A and B : all criteria should be fulfilled.
HTN, hypertension.
[a]Stage C : At least 1 criteria should be fulfilled.
[b]Stage D : At least 1 criteria should be fulfilled.

5.2. Cirrhosis absent :

a. Characteristic tumour (arterial hypervascularisation) on US or CT or MRI and αFP level above 400 ng/mL : *Diagnosis of HCC* (45)
b. Other situation : biopsy. However a biopsy should be avoided in a potential curable patient considering the risk of needle tract seeding.

6. The risk of needle tract seeding after liver biopsy from HCC

The puncture of a hepatocellular carcinoma, either in the context of a diagnostic procedure or a therapeutic intervention (e.g. percutaneous radiofrequency ablation (RFA) or ethanol injection (PEI)), carries a substantial risk of needle tract seeding. The incidence of needle tract seeding was 1.6% in 122 patients who had ultrasound guided diagnostic biopsy in a HCC before they underwent surgery (46). Needle tract seeding was reported to be 3.4% (7 of 205 cases) by Kim *et al.* (47) , and 5.1% (3 of 59 cases) by Takamori *et al.* (48). Tumour seeding after percutaneous RFA varied between 0-12.5% in several series (49). These differences may partly result from differences in follow-up time (as it may take 18 months before a metastasis in a needle tract is detected) and the use of different needles. In PEI and especially RFA larger needles are used and multiple punctures are applied, probably substantially enhancing the risk of seeding, in comparison to fine needle biopsy. Thermocoagulation of the needle track at the end of treatment did not prevent needle track seeding in a case report (50).

Recommendation : biopsy from HCC

Whenever a curative lesion is present, biopsy of potentially operable lesions should be avoided because of the risk of needle tract seeding. However in the individual case where a biopsy is needed, the following points should be taken into account : In this approach a small, but definite risk of seeding exists. This risk could be diminished by the use of a fine needle biopsy. However the rate of false negatives could be higher by the use of this technique where a smaller tissue sample is preserved. The risk of needle tract seeding should be balanced against the risk of an unnecessary treatment.

7. Assessment of disease extension

Cancer staging should serve to select the appropriate primary and adjuvant therapy and to estimate the prognosis. It is also of use in the evaluation of treatment results.

In oncology, the prognosis of patients with solid tumours is solely related to tumour stage. HCC constitutes a particular neoplasm. The cirrhosis that is present in most cases determines the applicability and efficacy of treatment and hence has an important influence on prognosis.

According to the EASL panel of experts (43), prognosis of HCC is determined by the tumour stage, the general health of the patient, the liver function of the patient and the treatment efficacy. Staging systems assessing just one of these aspects such as the Child-Pugh classification (51), TNM classification (52) and performance status (53), have therefore only a marginal usefulness.

Several staging systems for HCC have been developed, using two, three or four of the above mentioned factors. There is no agreement on the best staging system that can be recommended world-wide.

The Barcelona-Clinic Liver Cancer (BCLC) staging system (54) uses variables related to tumour status, liver functional status, physical status, and links the four stages (Table 1) described with a treatment logarithm (fig. 1). It has been suggested that the system is able to select early-stage patients that could benefit from curative therapies (55). At present, it has no external validation.

Before any decision is made for treating a patient with HCC, the following questions have to be addressed :

- What is the status of the non-tumourous liver ?
- What is the size and extension of the tumour ?
- What is the general condition of the patient ?

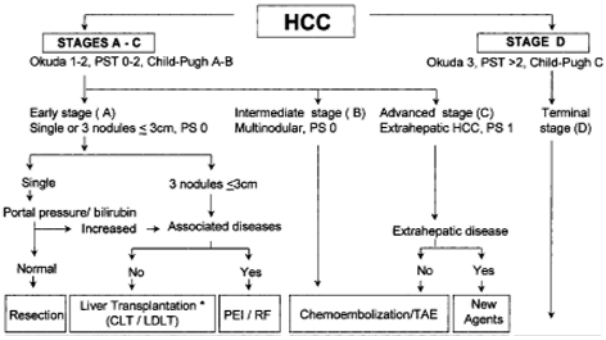

Fig. 1. — Adapted to BCLC (Barcelona Clinic Liver Cancer) staging system. PS = performance Scale (0 : normal activity, 1 : symptoms but nearly fully ambulatory, 2 : some bed time, but needs to be in bed in less than 50% of normal daytime, 3 : needs to be in bed greater than 50% of normal day time, 4 : Unable to get out of bed) [(reprinted from 'Prognostic prediction and treatment strategy in hepatocellular carcinoma' Hepatology vol 35, 519-524, 2002 with permission from the American Association for the Study of Liver Diseases and with permission from the authors (Bruix and Llovet)].

7.1. *Status of the non-tumourous liver*

In Europe, 85-90% of patients with HCC have a cirrhotic liver and most of the remaining have an underlying liver disease.

- Patient with non-cirrhotic liver are the best candidates for resection or other therapeutic means that could damage liver function, such as chemo-embolization.
- HCC patients with decompensated cirrhosis are not eligible for any invasive (radiological or surgical) method. The first option here is liver transplantation.

7.2. *Evaluation of tumour extension*

Evaluation of tumour extension is necessary in all cases and includes a search for the presence of daughter nodules and/or portal vein thrombosis. This could be done by US, spiral CT scan and/or MRI. CT should be done with latest generation equipment, using thin liver slices without contrast and during the arterial, venous and equilibrium phases of contrast administration. The use of lipiodol CT is not recommended because of its limited accuracy. Dynamic MRI may substitute for CT scanning.

The improvements in CT and MRI equipment have reduced the clinical usefulness of angiography.

In selected cases, extrahepatic spread should be searched for by thin section spiral CT of the chest and bone scintigraphy. The usefulness of positron emission tomography (PET scan) is not established in HCC.

7.3. *The patient's general condition*

The patient's general condition must be assessed before taking any therapeutic decision. This should be analysed by means of the Karnofsky index or performance status, which will identify patients with advanced or terminal disease that are not eligible for most of the procedures. In case of liver transplantation, variables dependent on liver failure, even involving the general status, are less relevant, although they might increase the peri-operative mortality. In this case, assessment of cardiovascular and pulmonary function and of other systemic conditions is crucial.

Recommendations

- Staging of HCC should take into account the liver function of the patient, the extent of the tumour and the general condition of the patient.
- It should be established whether the patient has underlying cirrhosis, and if so, what is the liver function.
- US, spiral CT and/or dynamic MRI of the liver should be used to evaluate tumour size, the presence of daughter nodules and the presence of portal vein thrombosis. Extrahepatic spread should be searched for by chest thin section spiral CT and bone scintigraphy.
- The general condition of the patient should be evaluated using the Karnofsky index or performance status.
- If liver transplantation is considered, assessment of cardiovascular and pulmonary function and other systemic conditions is essential.

8. Transplantation or resection in patients with HCC

The only proven potentially curative therapy for HCC remains surgery, either hepatic resection for a HCC in a non-cirrhotic liver or liver transplantation for patients having a HCC in a cirrhotic liver. Patients with single small HCC (< 5 cm) or up to three lesions < 3 cm should be referred for assessment for these treatment modalities (56-59). In all of these cases extra hepatic metastases, hilar lymph adenopathies and tumoural portal thrombosis exclude the possibility for a curative option. However, there are no randomised trials comparing the outcome of surgical resection and liver transplantation for HCC. Surgical resection and percutaneous treatment modalities in patients with cirrhosis have the disadvantage that the remnant liver remains a premalignant condition with the potential to develop new HCC lesions in this part of the liver.

8.1. *Resection*

Hepatic resection is the first-line approach for non-cirrhotic patients with HCC. This applies to less than 5% of the cases in the West and in Belgium (45). In the majority of the cases the tumour is fibrolamellar and has a very different biology in comparison with the HCC arising in a cirrhotic liver. In the absence of cirrhosis, surgical resection of this tumour is less likely to produce liver failure. In most of the series, liver resection achieved similar results in survival and disease-free survival as compared to transplantation. Liver resection

remains the treatment of choice in those patients with fibrolamellar HCC in a non-cirrhotic liver.

In cirrhotic patients, the poor selection of candidates for resection in the eighties led to unacceptable survival rates below 50% at 3 years (60). To avoid these treatment-related complications such as post operative liver failure, selection has been refined to patients with a single HCC and a well preserved liver function (Child Pugh A) with a normal bilirubin level and the absence of portal hypertension (defined as the presence of oesophageal varices, platelet count of less than 100,000/µl or splenomegaly). Subjects without relevant portal hypertension and normal bilirubin levels achieved a 70% survival at 5 years, whereas this decreased to 50% in patients with portal hypertension and to 25% in patients with portal hypertension and abnormal bilirubin levels (61). 'Ideal' candidates constitute only a minority in Western countries.

8.2. *Transplantation*

Early results of liver transplantation for HCC were poor with 5 year survival rates below 50%, mainly due to tumour recurrence (60). This was the result of poor selection of patients for transplantation. It is well established that patients with single lesions of less than 5 cm or up to 3 lesions less than 3 cm in the absence of vascular invasion, have a low recurrence rate for HCC and the prognosis after transplantation is the same as for a similar underlying liver disease without HCC (57-59). Resection of HCC is a viable option, with short term survival rates similar to transplantation (61,62). After three years of follow up, there is a clear advantage for transplantation in terms of tumour free survival (62).

At present, the shortage of donors led to extremely long waiting times. Programs in the United States, Europe and Belgium face a waiting time of over 12 months. The drop out rate on the waiting list is therefore great. This event is also common in patients listed with HCC. In the United States, the UNOS have adopted the Model for End-Stage Liver Disease (MELD) system to allocate grafts according a composite score, which includes bilirubin, prothrombin activity and creatinine levels for non-cancer patients. This model answers to the principle : sickest patient first. However patients with HCC frequently have a rather good liver function and a low MELD score. To avoid undesirable long waiting list time in HCC patients a variable score between 24 and 29 points was given to these patients (63).

Living donor liver transplantation (LDLT) has emerged as a feasible alternative to cadaveric transplantation. Decision analyses have shown that LDLT is cost-effective for early HCC in comparison to cadaveric transplantation when waiting time exceed 7 months (64). However, the absence of donor constraints is counteracted by the fact that the procedure is associated with a 0.5% mortality rate of the donor, and around 20% morbidity.

The standard criteria (1 lesion less than 5 cm, 3 lesions each less than 3 cm) have recently been questioned with similar survival rates in patients with larger tumours and even in the presence of intrahepatic portal involvement. In the era of shortage of organs, these 'expanded criteria' should be considered as unfair until more evidence is present about the long term outcome of these patients. On the contrary, the principle of expanded criteria may apply to LDLT, considering the unlimited availability of this procedure as well as the almost non-existent waiting time. A set of new expanded criteria have been proposed and are expected to achieve 50% 5 year survival rates in patients with either single tumours < 7 cm, 3 nodules < 5 cm, 5 nodules < 3 cm, or downstaging to conventional criteria after any therapy lasting more than 6 months (65). However data at this moment are small to conclude these criteria will become the standard in patients waiting for LDLT.

Recommendations

The only proven potentially curative treatment for HCC remains surgery, either hepatic resection for patients with a HCC in a non-cirrhotic liver or liver transplantation for patients with a HCC in a cirrhotic liver. Patients with single small HCC (< 5 cm) or up to three lesions should be referred for these treatment modalities. Surgical resection and percutaneous treatment modalities in patients with cirrhosis have the disadvantage that the remnant liver remains a premalignant condition with the potential to develop new HCC lesions in this part of the liver.

- Liver transplantation should be considered in any patient with cirrhosis and a small (5 cm or less single nodule or up to three lesions of 3 cm or less) HCC.
- Hepatic resection should be considered as primary therapy in any patient with HCC and a non-cirrhotic liver (including fibrolamellar variant).
- Resection can be carried out in highly selected patients with hepatic cirrhosis and well preserved hepatic function (Child Pugh A). Such surgery carries a high risk of postoperative decompensation and should be undertaken in units with expertise in hepatic resection and management of liver failure.
- If surgery or transplantation is not possible, percutaneous treatment modalities can be used as an alternative.

9. Percutaneous treatments

Percutaneous treatments are considered as minimally invasive procedures that constitute the best medical option for non-surgical HCC. Tumour ablation is achieved by using chemical substances (alcohol, acetic acid), or by modifying the temperature of the neoplastic cells (radiofrequency, microwave, laser, and cryoablation) (45).

Percutaneous ethanol injection (PEI) achieves complete responses of 70% in HCC < 3 cm, and is considered the gold standard percutaneous treatment (65). Child Pugh A patients with complete responses achieve 5 year survival rates of 50%. Outcome is worse in Child B and C patients (66). Radiofrequency ablation (RFA) is the most extensively used alternative to PEI, either trough single or multiple cooled-tip electrodes, or single electrode associated with J-hook needles, according to different engines available. It can also be used during laparotomy or during laparascopy. RFA may provide marginal anti-tumoural effects in tumours larger than 3 cm in diameter where PEI is unable to disrupt the intratumoural septa (45). At present the 5 year survival rate estimate from a cohort of 88 patients with tumours smaller than 3.5 cm treated by RFA is 33% (67). A recent randomised controlled trial of 102 patients with cirrhosis and either single HCC 5 cm in diameter or smaller or as many as 3 HCCs each 3 cm or smaller randomly tretad with RFA or PEI showed superiority of RFA treatment with respect to local recurrence-free survival rates (68). There is a need for further randomised trials comparing the efficacy of the cheaper PEI versus the more expensive RFA.

The assessment of treatment response is important. The EASL panel of experts of HCC proposed a modification of the WHO criteria : 1) assessment of response by spiral CT or MRI 4 weeks after treatment, 2) measurements of the diameter refer to the viable tumour (identified by the area enhanced during spiral CT), rather than changes in the overall diameter and 3) local recurrences should be defined as treatment failures (43).

Recommendations

- Percutaneous ethanol injection has been shown to produce necrosis of small HCC. It is best suited to peripheral lesions, less than 3 cm in diameter. Radiofrequency ablation may be a good alternative ablative therapy but data are limited.
- Percutaneous treatment modalities in patients with cirrhosis have the disadvantage that the remnant liver remains a premalignant condition with the potential to develop new HCC lesions in this part of the liver.

10. Arterial chemoembolization, chemotherapy and hormonal therapy

Most patients with HCC are diagnosed at advanced stages. There is no standard treatment for patients with unresectable HCC, despite the availability of many prospective trials during the last 25 years. Therapies include single interventions or combinations of systemic chemotherapy, intra-arterial chemotherapy, arterial devascularization (embolization) and hormonal manipulation (tamoxifen, octreotide).

Llovet *et al.* (69) recently reviewed 61 small RCTs dealing with primary treatment of HCC and could perform a reliable meta-analysis for only two types of intervention : embolization/chemoembolization (7 trials, 545 patients) and tamoxifen (7 trials, 898 patients). From their meta-analysis, they concluded the following :

– Arterial chemoembolization improved 2-year survival compared with control (41% vs. 27%). There was a significant benefit of chemoembolization with cisplatin or doxorubicin but none with embolization alone. Overall, treatment induced objective responses in 35% of patients (range, 16%-61%).

The side effects of this chemoembolization procedures include those of the chemotherapeutic agent and the complications of arterial embolization (liver failure, pain, fever). Serious complications arise in up to 5% of patients and there are no studies evaluating quality of life. Portal vein thrombosis is a contra-indication for embolization. Patients with well-preserved liver function (Child-Pugh A) and multinodular HCC without vascular invasion or extrahepatic spread, seem the best target population.

– Tamoxifen showed no antitumoral effect and no effect on survival, and only low-quality trials suggested 1-year improvement in survival.

There is no available evidence (69) to withhold or to give other palliative interventions and therefore the following interventions should only be offered to the patients in the context of well-designed clinical trials :

– Systemic chemotherapy has been studied in 9 RCTs (45). The best single agents are doxorubicin and cisplatin, with partial responses in 5-15% of cases. Only 2 studies had a no-treatment arm, but showed no survival benefit.

– A small RCT of subcutaneous octreotide therapy has suggested a survival benefit in HCC. However, a subsequent study of 70 patients treated with long acting octreotide showed no benefit.

Recommendations

- Chemoembolization (with doxorubicin or cisplatin) prolongs life in a subset of patients (preserved liver function) with unresectable HCC in controlled clinical trials .
- Hormonal therapy with tamoxifen has shown no survival benefit in controlled trials and is not recommended.
- Systemic chemotherapy and/or hormonal interventions (e.g. octreotide) should only be offered in the context of clinical trials.

11. Radioactive Iodine 131 treatment

Via intra arterial way, a mixture of radioactive Iodine 131 and Lipiodol is instilled in the HCC. The patients are to be isolated after each procedure as a radioactivity safety measure. A small randomised trial in patients with HCC and portal vein thrombosis demonstrated a limited

benefit in survival. A larger trial comparing arterial chemoembolization and radioactive Iodine 131 treatment did not show any difference in survival between the two groups. However, side effects were significantly lower in the group receiving radioactive Iodine 131 treatment.

Radioactive Iodine 131 treatment was also used in a adjuvant setting in patients resected for HCC without detectable residual disease. A longer delay of recurrence was observed in the treated group (70).

Recommendations

The use of radioactive Iodine 131 treatment can be used as an alternative for chemoembolization.

12. Treatment of early hepatocellular carcinoma in patients on the waiting list for liver transplantation

Liver transplantation is the therapy of choice for cirrhotic patients with early hepatocellular carcinoma (HCC). The optimal candidates for liver transplantation (single nodule < 5 cm or up to 3 nodules < 3 cm) achieve a 70% 5-year survival rate, with recurrence rate below 15% (59). The prognosis after transplantation is therefore the same as for a similar underlying disease without HCC. However, these excellent results were obtained at a time when the average waiting time for liver transplantation was less than 6 months. But the tumour doubling time in asymptomatic HCC less than 5 cm was estimated to be around 4 months (71). Therefore, the delay between diagnosis and transplantation can allow the tumour to grow to stages that contraindicate transplantation. In a time when the shortage of donors has led to longer waiting time (leading programs of transplantation in Europe and in the United States face a waiting time of over 12 months), the results of liver transplantation are expected to be sharply worsened in intention-to-treat analysis. It has been shown that a waiting time longer than six months was associated with a 23% rate of dropout from the waiting list, usually because of progression of HCC (64). The dropout rates for a waiting time of one year were as high as 50%.

Several strategies (chemoembolization, ethanol percutaneous ablation or radiofrequency ablation) have been proposed to control HCC while awaiting transplantation. Living donor liver transplantation which provides the advantage of avoiding a waiting list or resection followed by salvage cadaveric transplantation have also been proposed.

The benefits of these procedures for reducing the dropout rate or for modifying the outcome are unknown as prospective randomized controlled trials are lacking. However, some practical recommendations can be suggested, with stratification according to the expected waiting time on the list (parameter mostly influenced by the patient's Child-Pugh score).

If the expected waiting time is over 3 months, percutaneous ethanol injection is probably the best strategy. A decision analysis has shown that percutaneous ethanol injection increases the probability of being transplanted and confers a survival advantage compared with conservative management, and this, since the start of the waiting period before transplantation (72).

On the opposite, the use of RFA, an effective procedure to control tumour, is discouraged prior to liver transplantation. There are concerns, indeed, about the risk of tumour seeding (Lvovet recorded as many as 12.5% of needle-track seeding after this procedure), an unacceptable risk in this subset of patients for whom a curative therapy is possible (73). It has to be stressed that in this series seeding occurred always in subcapsular tumours treated with multiple punctures, without tract ablation. Other studies much lower seeding rates, comparable with PEI using a transhepatic approach, avoiding multiple punctures and applying liver and parietal tract ablation (68,74,75).

Chemoembolization is a common adjuvant treatment for patients on the waiting list. This option contributes to accurate staging of the intrahepatic disease and may achieve extensive tumor necrosis (76-80). The procedure is well tolerated in the majority of this subset of patients waiting for transplantation. Furthermore, it has been shown that the prevalence of hepatic arterial thrombosis, a graft-threatening complication of transplantation, was not increased in patients who underwent hepatic arterial chemoembolization before transplantation (76). It is probably the treatment of choice during the waiting list for patient with Child A cirrhosis when percutaneous injection is not feasible.

If the waiting time before transplantation is expected to be shorter than 3 months, the interest of adjuvant therapies is probably clinically less relevant.

If the waiting list exceeds seven months, a decision analysis has shown that living donor liver transplantation is cost effective compared with cadaveric transplantation (66).

Decision analysis has also shown that surgical resection while waiting for transplantation for patients with single HCC and well preserved hepatic function provides moderate gains in life expectancy and is cost effective only if the waiting list exceeds one year (72).

According to the available data, the following decision tree could be proposed for cirrhotic patients with early HCC.

Recommendations

There are no randomized trials comparing different treatment options for the HCC patient on the liver transplant waiting list. Every transplantation center has different habits in the treatment of these patients. No distinct guidelines can be given here. Fig 2 only illustrates a possible approach for these patients.

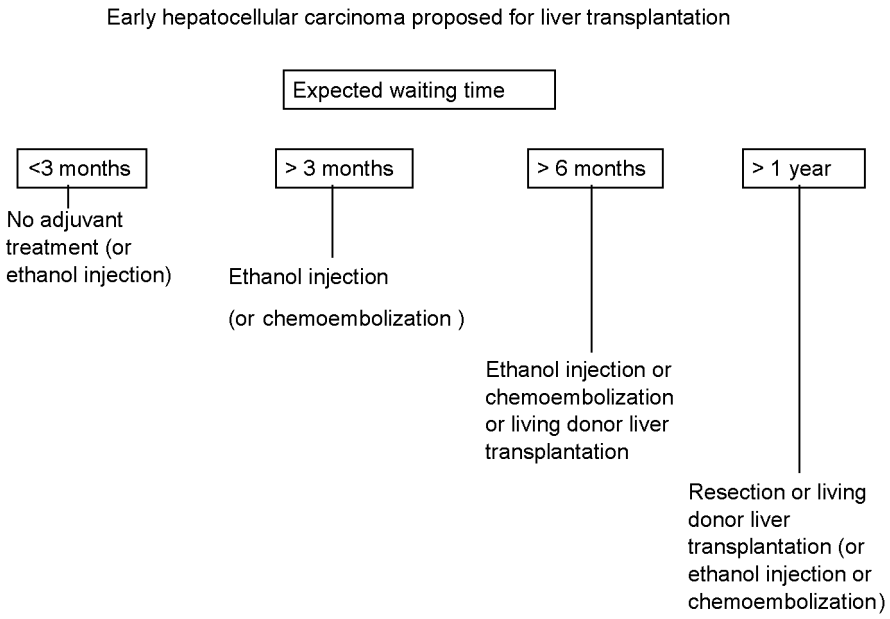

Fig. 2. — Proposal for the approach of the HCC patient on the waiting list

References

1. LONDON T., MEGLYNN K. Liver cancer. In : SCHOTTENFELD D., FRAUMENI J. Cancer epidemiology and prevention, Oxford University Press, New-York, 1996.
2. MEGLYNN K., TSAO L., HSING A., DEVESA S., FRAUMENI J. International trends and patterns of primary liver cancer. *Int. J. Cancer*, 2001, **90** : 290-296.
3. EL-SERAG H., MASON A. Rising incidence of hepatocellular carcinoma in the United States. *N. Engl. J. Med.*, 1999, **340** : 745-750.
4. EL-SERAG H., MASON A. Risk factors for the rising rates of primary liver cancer in the United States. *Arch. Intern. Med.*, 2000, **180** : 3227-3230.
5. CHANG M.H., CHEN C.J., LAI M.S., HSU H.M., WU T.C., KONG M.S., LIANG D.C., SHAU W.Y., CHEN D.S. Universal hepatitis B vaccination in Taiwan and the incidence of hepatocellular carcinoma in children. Taiwan Childhood Hepatoma Study Group. *N. Engl. J. Med.*, 1997, **336** : 1855-9.
6. CHANG M.H., SHAU W.Y., CHEN C.J., WU T.C., KONG M.S., LIANG D.C., HSU H.M., CHEN H.L., HSU H.Y., CHEN D.S. The Taiwan Childhood Hepatoma Study Group. Hepatitis B vaccination and hepatocellular carcinoma rates in boys and girls. *J. Am. Med. Assoc.*, 2000, **284** : 3040-2.
7. NIEDERAU C., HEINTGES T., LANGE S., GOLDMANN G., NIEDERAU C.M., MOHR L. *et al.* Long-term follow-up of HBeAg-positive patients treated with interferon alfa for chronic hepatitis B. *N. Engl. J. Med.*, 1996, **334** : 1422-7.
8. LIN S.M., SHEEN I.S., CHIEN R.N., CHU C.M., LIAW Y.F. Long-term beneficial effect of interferon therapy in patients with chronic hepatitis B virus infection. *Hepatology*, 1999, **29** : 971-5.
9. CAMMÀ C., GIUNTA M., ANDREONE P., CRAXI A. Interferon and prevention of hepatocellular carcinoma in viral cirrhosis : an evidence-based approach. *J. Hepatol.*, 2001, **34** : 593-602.
10. KASAHARA A., HAYASHI N., MOCHIZUKI K., TAKAYANAGI M., YOSHIOKA K., KAKUMU S., IIJIMA A., URUSHIHARA A., KIYOSAWA K., OKUDA M., HINO K., OKITA K. Risk factors for hepatocellular carcinoma and its incidence after interferon treatment in patients with chronic hepatitis C. Osaka Liver Disease Study Group. *Hepatology*, 1998, **27** : 1394-402.
11. CAMMÀ C., DI MARCO V., LO IACONO O., ALMASIO P., GIUNTA M., FUSCHI P., VACCARO A., FABIANO C., MAGRIN S., STEFANO R., BONURA C., PAGLIARO L., CRAXI A.. Long-term course of interferon-treated chronic hepatitis C. *J. Hepatol.*, 1998, **28** : 531-7.
12. YOSHIDA H., SHIRATORI Y., MORIYAMA M., ARAKAWA Y., IDE T., SATA M., INOUE O., YANO M., TANAKA M., FUJIYAMA S., NISHIGUCHI S., KUROKI T., IMAZEKI F., YOKOSUKA O., KINOYAMA S., YAMADA G., OMATA M. Interferon therapy reduces the risk for hepatocellular carcinoma : national surveillance program of cirrhotic and noncirrhotic patients with chronic hepatitis C in Japan. IHIT Study Group. Inhibition of Hepatocarcinogenesis by Interferon Therapy. *Ann. Intern. Med.*, 1999, **131** : 174-81.
13. COLOMBO M. Screening for cancer in viral hepatitis. *Clin. Liver Dis.*, 2001, **5** : 109-121.
14. NGUYEN M., KEEFFE E. Screening for hepatocellular carcinoma. *J. Clin. Gastroenterol.*, 2002, 35.
15. JOHNSON P., WILLIAMS R. Cirrhosis and the etiology of hepatocellular carcinoma. *J. Hepatol.*, 1987, **4** : 140-147.
16. CALVET X., BRUIX J., BRU C., GINES P., VILANA R., SOLE M., AYUSO M., BRUGUERA M., RODES J. Natural history of hepatocellular carcinoma in Spain. *J. Hepatol.*, 1990, **10** : 311-317.
17. THE CANCER OF THE LIVER ITALIAN PROGRAM (CLIP) INVESTIGATORS. A new prognostic system for hepatocellular carcinoma : A retrospective study of 435 patients. *Hepatology*, 1998, **28** : 751-755.
18. OMATA M., TAKANO S. Occurrence of hepatocellular in chronic viral hepatitis. *Cancer Chemother. Pharmacol.*, 1994, **33** (suppl) : S 153-S 154.
19. BRECHOT C., JAFFREDO F., LAGORCE D., GERKEN G., MEYER ZUN BÜSCHENFELDE K., PAPAKONSTONTINOU A., HADZIYANNIS S., ROMEO R., COLOMBO M., RODES J., BRUIX J., WILLIAMS R., NAOUMOV N. Impact of HBV, HCV and GBV-C/HGV on hepatocellular carcinoma in Europe : results of an european concerted action. *J. Hepatol.*, 1998, **29** : 173-183.
20. LIA Y.-F., TAI D.-I., CHU C.-M., LIN D.-Y., SHEEN I.-S., CHEN T.-J., PAO C.C. Early detection of hepatocellular carcinoma in patients with chronic type B hepatitis – A prospective study. *Gastroenterology*, 1986, **90** : 263-267.
21. SHERMAN M., PELTEKIAN K., LEE C. Screening for hepatocellular carcinoma in chronic carriers of hepatitis B virus : incidence and prevalence of hepatocellular carcinoma in a North America urban population. *Hepatology*, 1995, **22** : 432-438.
22. IKEDA K., SAITOH S., SUZUKI Y., KOBAYASHI M., TSUBOTA A., KOIDA I., ARASE Y., FUKUDA M., CHAYAMA K., MURASHIMA N., KUMADA H. Disease progression and hepatocellular carcinogenese in patients with chronic viral hepatitis : a prospective observation of 2218 patients. *J. Hepatol.*, 1998, **28** : 930-938.
23. YANG H.-I., LU S.-N., LIAW Y.-F., YOU S.-L., SUN C.-A., WANG L.-Y., HSIAO C., CHEN P.-J., CHEN D.-S., CHEN C.-J. Hepatitis B e antigen and the risk of hepatocellular carcinoma. *N. Engl. J. Med.*, 2002, **347** : 168-174.
24. TSUKUMA I., HIYANA T., TANAKA S., NAKAO H., YABUUCHI T., KITANURA T., NAKANISHI K., FUJIMOTO I., INOUE A., YANAZAKI H., KAWASHIMA T. Risk factors for hepatocellular carcinoma among patients with chronic liver disease. *N. Engl. J. Med.*, 1993, **328** : 1797-1801.

25. LOK A., LAI C.-L. Factors determining the development of hepatocellular carcinoma in hepatitis B surface antigen carriers. *Cancer*, 1988, **61** : 1287-1291.
26. HENRION J., DE MAEGHT S., DELTENRE P., CHILAIN J.-M., MAISIN J.-M., SCHAPIRA M., HELLER F. Impact of hepatitis C virus infection on the aetiology of cirrhosis and hepatocarcinoma in the affiliated hospitals in Southern Belgium. *Acta Gastroenterol. Belg.*, 2002, **65** : 80-82.
27. HENRION J., LIBON E., DE MAEGHT S., DELTENRE P., SCHAPIRA M., GHILAIN J.-M., MAISIN J.-M., HELLER F. Dépistage du carcinome hépatocellulaire dans une cohorte de malades porteurs d'une cirrhose d'origine principalement alcoolique. *Gastroenterol. Clin. Biol.*, 2003, **27** : 534-539.
28. VAN GOSSUM A., DUBOIS P., LAURENT E., REDING P., BURETTE A., ADLER M., CREMER M. Les caractéristiques cliniques, biologiques et épidémiologiques des hépatocarcinomes dans la région bruxelloise. *Acta Gastroenterol. Belg.*, 1985, **48** : 337-351.
29. CALVET X., BRUIX J., GINES P., BRU C., SOLE M., VILANA R., RODES J. Prognostic factors of hepatocellular carcinoma in the west : a multivariate analysis in 206 patients. *Hepatology*, 1990, **12** : 753-763.
30. OKUDA K., OHTSUKI T., OBATA H., TOMINATSU M., OKAZAKI N., HASEGAWA H., NAKAJIMA Y., OHNISHI K. Natural history of hepatocellular carcinoma and prognosis in relation to treatment. Study of 850 patients. *Cancer*, 1985, **56** : 912-928.
31. COLOMBO M. The natural history of hepatocellular carcinoma in western countries. *Hepato-Gastroenterol*., 1998, **45** : 1221-1225.
32. TAKETA K. α-foetoprotein : reevaluation in hepatology. *Hepatology*, 1990, **12** : 1420-1432. .
33. SHERMAN M. α-foetoprotein : an obituary. *J. Hepatol.*, 2001, **37** : 603-605.
34. IKEDA K., SAITOH S., KOIDA I., ARASE Y., TSUBOTA., CHAYAMA K., KUMADA H., KAWANISHI N. A multivariate analysis of risk factors for hepatocellular carcinogenesis : a prospective observation of 795 patients with viral and alcoholic cirrhosis. *Hepatology*, 1993, **18** : 47-53.
35. OKA H., TAMORI A., KUROKI T., KOBAYASHI K., YAHAMOTO S. Prospective study of α-foetoprotein in cirrhotic patients monitored for development of hepatocellular carcinoma. *Hepatology*, 1994, **19** : 61-66.
36. OKANO H., SHIRAKI K., INOUE H., ITO T., YAMANAKO T., DEGUCHI M., SUGIMOTO K., SAKAI T., OHMORI S., MURATA K., TAKASE K., NAKANO T. Comparison of screening methods for hepatocellular carcinoma in patients with cirrhosis. *Anticancer Research*, 2001, **21** : 2979-2982.
37. ZOLI M., MAGALOTTI D., GUELLI C., MARCHESINI G., PISI E. Efficiency of a surveillance program for early detection of hepatocellular carcinoma. *Cancer*, 1996, **78** : 977-985.
38. COLOMBO M., DE FRANCHIS R., DEL NINNO E., SANGIOVANNI A., DE FAZIO C., TOMMASINI M., DONATO F., PIVA A., DI CARLO V., DIOGUARDI N. Hepatocellular carcinoma in Italian patients with cirrhosis. *N. Engl. J. Med.*, 1991, **325** : 6.
39. PATERON D., GANNE N., TRINCHET J-C., AUROUSSEAU M-H., MAL F., MEICLER C., CODERC E., REBOULLET P., BEAUGRAND M. Prospective study of screening for hepatocellular carcinoma in Caucasian patients with cirrhosis. *J. Hepatol.*, 1994, **20** : 65-71.
40. COTTONE M., VIRDONE R., FUSCO G., ORLANDO A., TURRI M., CALTAGIRONE H., MARINGHINI A., SCIARRINO E., DEMMA I., NICOLI N., TINE F., SAMMARCO S., PAGLIARO L. Asymptomatic hepatocellular carcinoma in Child's A cirrhosis. A comparison of natural history and surgical treatment. *Gastroenterology*, 1989, **96** : 1566-1571.
41. FAIVRE J., FORMAN D., ESTEVE J., OBRADOVIC M., SANT M. and the EUROCARE working group. – Survival of patients with primary liver cancer, pancreatic cancer and biliary tract cancer in Europe. *Eur. J. Cancer*, 1998, **34** : 2184-2190.
42. EL-SERAG H., MASON A., KEY C. Trends in survival of patients with hepatocellular carcinoma between, 1977 and, 1996 in the United States. *Hepatology*, 2001, **33** : 62-65.
43. BRUIX J., SHERMAN M., LLOVET J.M., BEAUGRAND M., LENCIONI R., BURROUGHS A.K., CHRISTENSEN E., PAGLIARO L., COLOMBO M., RODES J. ; EASL PANEL OF EXPERTS ON HCC. Clinical management of hepatocellular carcinoma. Conclusions of the Barcelona-2000 EASL conference. European Association for the Study of the Liver. *J. Hepatol.*, 2001, **35** : 421-30.
44. HORIGOME H., NOMURA T., SASO K., ITOH M., JOH T., OHARA H.L. Limitations of imaging diagnosis for small hepatocellular carcinoma : comparison with histological findings. *J. Gastroenterol. Hepatol.*, 1999, **14** : 559-65.
45. LLOVET J.M., BEAUGRAND M. Hepatocellular carcinoma : present status and future prospects**.** *J. Hepatol.*, 2003, **38** (Suppl 1) : S136-S49.
46. DURAND F., REGIMBEAU J.M., BELGHITI J., SAUVANET A., VILGRAIN V., TERRIS B., MOUTARDIER V., FARGES O., VALLA D. Assessment of the benefits and risks of percutaneous biopsy before surgical resection of hepatocellular carcinoma. *J. Hepatol.*, 2001, **35** : 254-8.
47. KIM S.H., LIM H.K., LEE W.J., CHO J.M., JANG H.J. Needle-tract implantation in hepatocellular carcinoma : frequency and CT findings after biopsy with a 19.5-gauge automated biopsy gun. *Abdom. Imaging*, 2000, **25** : 246-50.
48. LIU C., FRILLING A., DERESKEWITZ C., BROELSCH CE. Tumor seeding after fine needle aspiration biopsy and percutaneous radiofrequency thermal ablation of hepatocellular carcinoma. *Dig. Surg.*, 2003, **20** : 460-463.
49. MULIER S., MULIER P., NI Y., MIAO Y., DUPAS B., MARCHAL G., DE WEVER I., MICHEL L. Complications of radiofrequency coagulation of liver tumours. *Br. J. Surg.*, 2002, **89** : 1206-22.
50. TAKAMORI R., WONG L.L., DANG C., WONG L. Needle-tract implantation from hepatocellular cancer : is needle biopsy of the liver always necessary *? Liver Transplantation*, 2000, **6** : 67-72.
51. PUGH R.N.H., MURRAY-LYON I.M., DAWSON J.L., PIETRONI M.C., WILLIAMS R. Transsection of the oesophagus for bleeding oesophageal varices. *Br. J. Surg.*, 1973, **60** : 646-9.
52. International Union against Cancer (UICC). TNM classification of malignant tumours. In : SOBIN L.H., WITTEKIND C.H. (eds). 5th ed. New York : Wiley-Liss, 1997 : 74-7.
53. SORENSEN J.B., KLEE M., PALSHOF T., HANSEN H.H. Performance status assessment in cancer patients. An inter-observer validation study. *Br. J. Cancer*, 1993, **67** : 773-5.
54. LLOVET J.M., BRU C., BRUIX J. Prognosis of hepatocellular carcinoma : the BCLC staging classification. *Semin. Liver Dis.*, 1999, **19** : 329-38.
55. BEFELER A.S., DI BISCEGLIE A.M. Hepatocellular carcinoma : diagnosis and treatment. *Gastroenterology*, 2002, **122** : 1609-19.
56. RYDER S.D. Guidelines for diagnosis and treatment of hepatocellular carcinoma in adults. *Gut*, 2003, **52** (Suppl III) : 1-8.
57. MAZZAFERRO V., REGALIA E., DOCI R., ANDREOLA S., PULVIRENTI A., BOZZETTI F., MONTALTO F., AMMANTUNA M., MORAHITO A., GENNARI L. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *N. Eng. J. Med.*, 1996, **334** (11) : 693-699.
58. MC PEAKE J.R., O'GRADY J.G., ZAMAN S., PORTMANN B., WIGHT D.G., CALNE R.Y., WILLIAMS R. Liver transplantation for primary hepatocellular carcinoma : tumour size and number determine outcome. *J. Hepatol.*, 1993, **18** : 226-234.
59. LLOVET J.M., BRUIX J., FUSTER J., CASTELLS A., GARCIA-VALDECASAS J.C., GRANDE L., FRANCA A., BRU C., NAVASA M., AYUSO M.C., SOLE M., REAL M.I., VILANA R., RIMOLA A., VISA J., RODES J. Liver transplantation for small hepatocellular carcinoma : the tumour node metastasis classification does not have prognostic power. *Hepatology*, 1998, **27** : 1572-1577.
60. RINGE B., PICHLMAYR R., WITTEKIND C., TUSCH G. Surgical treatment of hepatocellular carcinoma : experience with liver resection and transplantation in 19 198 patients. *Word J. Surg.*, 1999, **15** : 270-285.
61. BRUIX J., CASTELLS A., BOSCH J., FEU F., FUSTER J., GARCIA-PAGAN J.C., VISA J., BRU C., RODES J. Surgical resection of hepatocellular carcinoma in cirrhotic patients : prognostic value of preoperative portal pressure. *Gastroenterology*, 1996, **111** : 1018-1022.
62. LLOVET J.M., FUSTER J., BRUIX J. Intention to treat analysis of surgical treatment for early hepatocellular carcinoma : resection versus transplantation. *Hepatology*, 1999, **30** : 1434-1440.
63. FREEMAN R., WIESNER R., HARPER A., MC DIARMID S.V., LAKE J., EDWARDS E., MERION R., WOLFE R., TURCOTTE J., TEPERMAN L. UNOS/OPTN Liver disease severity score, UNOS/OPTN Liver and Intestine, and UNOS/OPTN pediatric transplantation committees. The new liver allocation system : moving toward evidence-based transplantation policy. *Liver Transpl.*, 2002, **8** : 851-858.
64. SARASIN F., MAJNO P., LLOVET J.M., BRUIX J., MENTHA G., HADENGUE A. A liver donor liver transplantation for early hepatocellular carcinoma : a cost-effectiveness perspective. *Hepatology*, 2001, **33** : 1073-1079.
65. BRUIX J., LLOVET J.M. Prognostic prediction and treatment strategy in hepatocellular carcinoma. *Hepatology*, 2002, **35** : 519-524.
66. LIVRAGHI T., GIORGIO A., MARIN G., SALMI A., DE SIO I., BOLONDI L., POMPILI M., BRUNELLO F., LAZZZARONI S., TORZILLI G. Hepatocellular carcinoma and cirrhosis in 746 patients : long term results of percutaneous ethanol injection. *Radiology*, 1995, **197** : 101-108.
67. BUSCARINI L., BUSCARINE E., DI STASI M., VALLISA D., QUARETTI P., ROCCA A. Percutaneous radiofrequency ablation of small hepatocellular carcinoma, long-term results. *Eur. Radiol.*, 2001, **11** : 914-921.

68. LENCIONE R.A., ALLGAIER H.P., CIONI D., OLSCHEWSKI M., DEIBERT P., CROCETTI L., LAUBENBERGER J., ZUBER I., BLUM H.E., BARTOLOZZI C. Small hepatocellular carcinoma in cirrhosis : randomised comparison of radio-frequency thermal ablation versus percutaneous ethanol injection. *Radiology*, 2003, **228** : 235-240.
69. LLOVET J.M., BRUIX J. Systematic review of randomized trials for unresectable hepatocellular carcinoma : Chemoembolization improves survival. *Hepatology*, 2003, **37** : 429-42.
70. TRINCHET J.C., GANNE-CARRIE N., BEAUGRAND M. Review article : intra-arterial treatments in patients with hepatocellular carcinima. *Aliment Pharmacol. Ther.*, 2003, **17** (Suppl. 2) : 111-118.
71. SHEU J., SUNG J., CHEN D., YANG P., LAI M., LEE C., HSU H., CHUANG C.N., YANG P.C., WANG T.H. Growth rates of asymptomatic hepatocellular carcinoma and its clinical implications. *Gastroenterology*, 1985, **89** : 259-266.
72. LLOVET J., MAS X., APONTE J., FUSTER J., NAVASA M., CHRISTENSEN E., RODÉS J., BRUIX J. Cost effectiveness of adjuvant therapy for hepatocellular carcinoma during the waiting list for liver transplantation. *Gut*, 2002, **50** : 123-128.
73. LLOVET J., VILANA R., BRU C., BIANCHI L., SALMERON J., BOIX L., GANAN S., SALA M., PAGES M., AYUSO C., SOLE M., RODES J., BRUIX J. The Barcelona Clinic Liver Cancer Group. Increased risk of tumor seeding after precutaneous radio frequency ablation for single hepatocellular carcinoma. *Hepatology*, 2001, **33** : 1124-1129.
74. FONTANA R.J., HAMIDULLAH H., NGHIEM H., GREENSON J.K., HUSSAIN H., MARRERO J., RUDICH S., MC CLURE L.A., ARENAS J. Percutaneous radiofrequency thermal ablation of HCC : a safe and affective bridge to liver transplantation. *Liver Transplantation*, 2002, **8** : 1165-1174.
75. LIVRAGHI T., SOLBIATI L., MELONI M.F., GAZELLE G.S., HALPERN E.F., GOLDBERG S.N. Treatment of focal liver tumors with percutaneous radio-frequency ablation : complications encountered in a multicenter study. *Radiology*, 2003, **226** : 441-451.
76. RICHARD H., SILBERZWEIG J., MITTY H., LOU W., AHN J., COOPER J. Hepatic arterial complications in liver transplant recipients treated with pretransplantation chemoembolisation for hepatocellular carcinoma. *Radiology*, 2000, **214** : 775-779.
77. MAJNO P., ADAM R., BISMUTH H., CASTAING D., ARICHE A., KRISSAT J., PERRINH., AZOULAY D. Influence of preoperative transarterial lipiodol chemoembolisation on resection and transplantation for hepatocellular carcinoma in patients with cirrhosis. *Ann. Surg.*, 1997, **226** : 688-703.
78. HARNOIS D., STEERS J., ANDREWS J., RUBIN J., PITOT H., BURGART L., WIESNER R., GORES G. Preoperative hepatic artery chemoembolisation followed by orthotopic liver transplantation for hepatocellular carcinoma. *Liver Transpl. Surg. Liver Transpl. Surg.*, 1999, **5** : 192-199.
79. OLDHAFER K., CHAVAN A., FRUHAUF N., FLEMMING P., SCHLITT H., KUBIN S., NASHAN B., WEIMANN A., RAAB R., MANNS M., GALANSKI M. Arterial chemoembolization before liver transplantation in patients with hepatocellular carcinoma : marked tumor necrosis but no survival benefit. *J. Hepatol.*, 1998, **29** : 953-959.
80. VENOOK A., FERRELL L., ROBERTS J., EMOND J., FRYE J., RING E., ASHER N.L., JAKE J.R. Liver transplantation for hepatocellular carcinoma : results with preoperative chemoembolization. *Liver Transpl. Surg. Liver Transpl. Surg.*, 1995, **1** : 242-248.