Diagnosis and treatment of hepatocellular carcinoma

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Abstract

Several advances have been produced in the diagnosis and treatment of patients with hepatocellular carcinoma. It is possible to diagnose the neoplasm at an early stage when radical treatment options may be applied. The criteria to apply them successfully have been refined and the expected outcome has been improved, but we still lack a useful treatment for the vast majority of patients who are still diagnosed at an advanced stage. Efforts have to be done during the next years to develop such an option (perhaps based on gene manipulation) and until then the management of this tumour will still constitute a challenge for physicians taking care of patients with this neoplasm. (Acta gastroenterol. belg., **1999**, 62, **410-414**).

Key words: hepatocellular carcinoma, diagnosis, prognosis, treatment.

The development of hepatocellular carcinoma (HCC) is one of the most frequent complications in the evolution of cirrhosis. Five per cent of the patients with compensated cirrhosis may be diagnosed with HCC if properly explored and the prevalence increases to 15-20% in subjects with variceal bleeding (1). Furthermore, follow-up investigations in cirrhotics have shown that the probability of developing an HCC is as high as 20% at 5 years (2,3,4). Thus, cirrhotics of any aetiology constitute the population at risk for HCC. However, male sex, age above 50 years, alcoholism, viral aetiology, high inflammatory activity and increased alpha-fetoprotein (AFP) imply a higher risk (5,6), while the value of dysplasia or architectural distortion (7) is controversial. This high risk in cirrhotics has prompted the engagement of screening programs aiming to detect HCC at an early stage when radical treatment may be applied (8). Screening is based on regular AFP determination and hepatic ultrasonography (US). However, AFP concentration usually remains within the normal range in patients with early HCC and cirrhotics may exhibit slight increases of AFP coinciding with episodes of viral reactivation (9). Therefore, the cost-effectiveness of AFP determination for early detection is dubious (10,11). Taking into account the data on tumour growth most authors suggest HCC screening should be done every 6 months and that it should be based on US examination associated or not to AFP determination. This policy should be applied only in those patients who would be treated if diagnosed with HCC and excludes patients with advanced liver diseases who are not candidates for transplantation.

Diagnosis and staging

The detection of a suspicious nodule during follow-up should prompt its characterisation to confirm the diagnosis, to stage the neoplasm and to indicate treatment. Some patients will exhibit very small nodules related to regenerative processes without malignant traits and thus, we engage additional explorations if the nodule exceeds 15 mm or if AFP is increased. HCC diagnosis may be set by US guided biopsy or increased AFP concentration. There is no agreement in defining the diagnostic cut-off value of AFP. We use 100 ng/ml if the concentration prior to the detection of the nodule was normal. The techniques to be used for staging depend on the treatment that may be offered. Small HCC suitable for surgery or percutaneous ablation justify an extensive evaluation with at least US and dynamic spiral CT. Lipiodol CT has been shown to provide misleading results (12) and thus, its use not advised. There are no studies showing that angiography and MRI provide a better staging accuracy and there is no consensus regarding the minimal staging prior to treatment indication. Thus, each group has to define the best policy according to their experience.

Prognostic evaluation

Some years ago, the prognosis after HCC diagnosis was extremely grim with a median survival of less than 3 months (13,14). The advancement of the time of diagnosis has increased the proportion of patients diagnosed at an asymptomatic stage and prompted a survival improvement even in the absence of effective treatment. Thereby, HCC patients diagnosed at an intermediate stage may achieve a median survival of 3 years (15). The patients prognosis depends on tumor stage and on the degree of liver function impairment due to the underlying cirrhosis. Thus, all the prognostic classifications take into account some of the parameters related to tumor stage (size, number of nodules, symptoms, impairment of the performance status or the Karnofsky index, AFP values) and to liver function (bilirubin, ascites, renal function, cholestasis, Child-Pugh class. However, both in the clinical setting and within research investigations it is preferable to use specific prognostic tools for each different evolutionary

stage and for each treatment option. Accordingly, the application of widely used classifications such as the Child-Pugh, the TNM or the Okuda (14) systems may be informative, but they can not be considered optimal.

Treatment

The first therapeutic options to be considered for HCC patients are surgical resection and liver transplantation. If surgery is considered not feasible, patients are evaluated for percutaneous ablation (16,17). These options may achieve the complete elimination of the disease, but unfortunately they may be applied in less than 25% of the individuals. The majority of the cases are considered for palliative options within prospective investigations and the rest is diagnosed at a terminal stage when they merely need symptomatic treatment.

In this review we expose our treatment schedule (Fig. 1), describing both the criteria and requirements for each of the therapeutic options and the outcomes that may be expected.

Surgical resection

There are no studies comparing resection vs. Orthotopic liver transplantation (OLT) and thus, there is no answer to which should be considered the first therapeutic option. Resection should aim to eliminate the HCC and the surrounding tissue since this area is the most frequent site of dissemination. Major lobectomies are contraindicated in patients with cirrhosis and thus, we select for surgery patients with well preserved liver function and solitary tumours without vascular invasion or extrahepatic spread. Patients fitting into this definition correspond to the group A of the Child-Pugh classification, but a large proportion of them will develop hepatic decompensation (namely ascites) after the operation with impairment of their survival (18). Japanese groups refine the selection by using the indocyanine green metabolic rate (19), but we have evidenced that postoperative decompensation is related to the presence of portal hypertension (20). Accordingly, resection should only be indicated in individuals with normal portal pressure (Fig. 1). Following this criteria the 5-year survival may exceed 70% (18,21), but this is hampered by a disease recurrence rate that may exceed 50% at 5 years. The presence of microscopic vascular invasion or additional nodules imply a higher recurrence risk, while tumour size is not so powerful (22). Chemoembolization prior to surgery has not shown any benefit. Two recent studies have suggested that retinoids administration or lipiodol coupled with I-131 may be useful in that regard (23,24) but confirmation is needed.

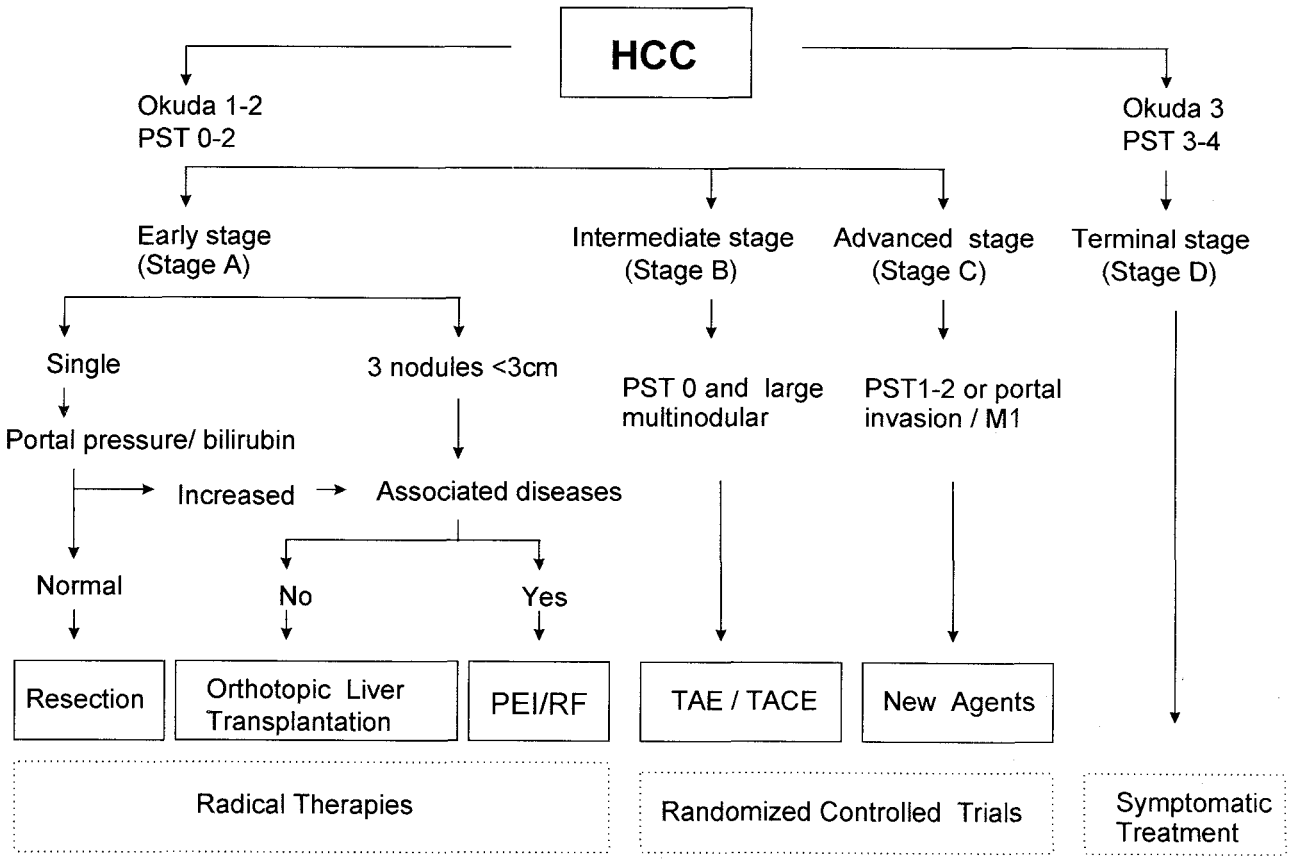

Fig. 1.

Orthotopic liver transplantation (OLT)

The initial results of OLT for HCC were disappointing. The majority of the patients were treated at an advanced stage and this induced a high recurrence rate and an unacceptable mortality (25). However, it was shown that patients with incidental tumours had the same survival as cirrhotics without HCC. Therefore, most programs restricted OLT indication to subjects with early HCC, a term that includes solitary HCC $\leq$ 5 cm or up to 3 nodules each one $<$ 3 cm. These criteria provide excellent results in terms of recurrence and survival and the main drawback of OLT is its applicability. There is a huge shortage of donors and while waiting for the liver, the HCC may progress and contraindicate the procedure. Some groups treat patients in the waiting list with chemotherapy, chemoembolization or ethanol injection or other percutaneous approach (26,27) but in the absence of randomised clinical trials (RCTs), it might be that the main determinant of success is the application of restrictive criteria, while treatment could not change the outcome (28).

Applying restrictive criteria, 5 year survival is around 70% (18,28,29) which compares with that after surgery in selected candidates, but the lower recurrence rate after OLT would favour this option. Nevertheless, the decision between both options should take into account that the survival may be the same and that there may be differences in terms of quality of life and the fact that HCV and HBV may infect the new liver and evolve to cirrhosis.

Percutaneous approach

Several techniques that can be used to treat tumoral nodules percutaneously, but the US guided ethanol injection (PEI) is the more widely used. Solitary nodules $<$ 3 cm will be almost always completely ablated (30) and the patients survival is the same as that of resected patients (31). Only surgical candidates with preserved liver function and normal portal pressure achieve a better outcome. Since resection eliminates the nodule and the surrounding satellites, it should be considered a better option than PEI. Furthermore, intraoperative US will detect unrecognised minute additional nodules, whose elimination should further reduce the risk of recurrence. and thus, improve the long term results.

PEI is highly effective in HCC $\leq$ 3 cm. Larger tumours may have septa that prevent the diffusion of ethanol. Injection of larger volumes (even under general anaesthesia), or the sequential treatment with arterial embolisation and PEI may increase the success rate, but the benefits of this approach are unclear. The treatment of patients with two or more nodules may be initially successful in some cases, but the failure and recurrence rates are higher.

PEI requires repeated injections to achieve the diffusion of the ethanol within the HCC. Boiling water (32) or acetic acid (33) have a better tissue penetration, but the manipulation of boiling water is not as easy, and the results obtained with acetic acid are similar to those obtained with PEI. The most promising alternative is the thermal ablation of the tumors by radiofrequency (34). This does not require an intratumoral diffusion and with only one treatment session it is possible to obtain complete necrosis the tumours. However, radiofrequency is more expensive and tumours located in the vicinity of the gall bladder or near to the diaphragm can not be treated. In fact, the complications rate and tolerance to radiofrequency are not as good as with PEI and therefore, carefully designed comparative studies are awaited.

Palliative Treatments

Patients who are not candidates for radical treatment are considered for palliative options. However, it has to be emphasised that none of the available options has been shown to improve the survival of the patients when assessed within randomised controlled trials and that most of the encouraging results have been raised by phase II trials in which the comparison has been made against an unrealistic natural history of untreated HCC as recently evidenced when reviewing the natural history of patients with non-surgical HCC. We have shown that the term non-surgical is too broad and includes two distinct subgroups : asymptomatic patients without portal invasion or extrahepatic spread will achieve a 50% survival at 3 years, while those without this profile achieve only a 20% (15).

Encouraging initial results that thereafter have not been confirmed have been observed with almost all options. Chemotherapy has never exceeded a 15% rate of positive responses with null impact on survival, even when given selectively coupled or not with lipiodol (35). The same applies for transarterial embolisation (TAE) through the injection of several agents (mostly gelfoam) combined or not with chemotherapy. TAE is considered for patients with patent portal blood flow and it prompts extensive tumour necrosis in most patients. However, recent trials have shown that it has no impact on survival (36,37,38). Another option that raised a huge interest was androgen and/or oestrogen blockade. Androgen blockade has never shown any benefit, but tamoxifen administration was suggested to improve the survival (39,40). Unfortunately, this has not been confirmed by large RCTs (41,42). Other treatment options such as interferon (43) or octreotide (44) have been suggested to be beneficial but the strength of the information is reduced and additional studies are needed.

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