Management of Hepatocellular Carcinoma

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Abstract
The aim of this review was to assess the correct clinical management of hepatocellular carcinoma (HCC). Following the diagnosis, the correct choice of treatment must take into account both the anatomical/biological features of HCC and the functional status of the underlying cirrhosis. As of today, only the application of the BCLC scoring system, which stratifies patients according to HCC staging and degree of liver disease in a process leading to a specific treatment, has shown the best results in terms of survival.

In the Western world, hepatocellular carcinoma (HCC) is strongly related to cirrhosis and this link is the postulate for surveillance programs among high-risk patients, even if surveillance would be recommended only in patients who would benefit from an effective treatment if diagnosed with HCC (survival is not significantly increased in screened patients with advanced cirrhosis – Child Pugh Class C). Ultrasound (US) and α-fetoprotein (α-FP) determination every 6 months are recommended for surveillance whose intervals remain controversial and clear evidence that 6 months is better than 12 is still lacking. However, the clinical usefulness of α-FP is debatable due to the very low positive predictive value and its limited sensibility. On the other hand, US has a sensitivity between 65 and 80% and a specificity >90% when used as a screening test [1]. The dynamic imaging tests utilized to diagnose HCC are based on the typical perfusion pattern of the HCC nodule, characterized by an early uptake of contrast medium during the arterial phase, followed by a rapid washout in the venous phase. One of the main factors affecting the sensitivity of the methods is the size of the lesion: according to the EASL guidelines, a lesion >2 cm can be defined as HCC (without the need of a biopsy) either if it shows the typical vascularization pattern in at least one imaging modality (CT scan or MRI, contrast US), or with α-FP levels >200 ng/ml. If the lesion is <1 cm, it should be followed with US at 3-month intervals: if the nodule remains stable over a period of 18–24 months, one can revert to routine surveillance; in case of growth, the nodule should be managed according to the size. With nodules between 1 and 2 cm, two concordant dynamic imaging tests showing the typical pattern are requested in order to make a diagnosis of HCC without a biopsy [2]. Prospective surveillance has increased the rate of detection of patients with early tumors, amenable for curative therapies. How-
ever, even the treatment of small lesions cannot be done irrespective of the underlying functional status of the cirrhotic liver. According to this, the ideal staging system should take into account tumor stage, liver function and patients’ performance status. Several prognostic staging systems have been proposed for HCC, but only BCLC (Barcelona Clinic Liver Cancer) accomplishes these aims at present. The greatest advantage of BCLC is that it is built to link staging with specific therapeutic options. The score stratifies patients in four groups with an increasing risk of death: (1) in group A (early stage), patients are included with a good performance status (PS = 0), with compensated liver disease (CPS A-B), asymptomatic, with either a single HCC ≤5 cm or up to 3 nodules ≤3 cm, susceptible to radical treatment (OLT, surgical resection and percutaneous treatment) with 50–75% 5-year survival rate; (2) patients with a large multinodular disease are defined as the intermediate stage (group B) and for them chemoembolization is the treatment of choice (3-year survival rates even without treatment may reach 50%); (3) for the advanced stage (patients with a PS 1–2, vascular invasion and/or extrahepatic spread) palliative treatments with new agents in the setting of randomized controlled trials are suggested (3-year survival rate is around 10%), and (4) finally, group D includes patients with a very poor life expectancy (stage 3 of Okuda’s classification or PS >2 or CPT C) for which solely symptomatic treatments are advocated [3]. Surgical resection is the main therapeutic choice for patients without cirrhosis or with compensated cirrhosis (CPT A), without portal hypertension and with normal levels of bilirubin. The optimal candidates can achieve a 5-year survival of 60–70%; however, only 5–10% of the patients eventually meet these requirements. On the other hand, tumor recurrence after surgical resection is expected in about 70% of the patients at 5 years (microvascular invasion, high grade of Edmonson score and satellite nodules are among the negative predictors for HCC recurrence) [4]. One critical point is the possibility that the choice of resection could expose to the risk of recurrences no longer treatable with OLT due to advance in tumor stage or advanced age. OLT enables to simultaneously cure both the tumor and the underlying cirrhosis in selected patients. The best candidates for LT (patients with single HCC ≤5 cm or up to 3 nodules ≤3 cm) can achieve a >70% survival at 5 years, with a recurrence rate <15%. However, the unavailability of this treatment worldwide and the shortage of donors can temper these excellent results and condition a high dropout rate among wait-listed patients (about 20% in waiting times exceeding 6 months) [5]. Living donor transplantation can be offered for HCC if the waiting time is long enough to allow tumor progression to lead to exclusion from the waiting list. In order to diminish tumor progression, adjuvant therapies (percutaneous ablation or chemoembolization) are performed in most transplant centers, even if there is no clear-cut evidence of benefit for these pre-OLT procedures. As of today, the priority in the waiting list is ruled by the severity of the liver disease. The MELD model predicts short-term (3 months) mortality in patients with cirrhosis. In order to ‘adapt’ the MELD scoring system to correctly prioritize HCC patients, in the UNOS area and in several liver transplant centers worldwide, substitutive points were assigned according to the stage of the HCC (an additional 10% point increase is given for every 3 months spent on the waiting list). Percutaneous treatments are the best medical option for non-surgical HCC. They are based on the injection of either chemical substances like ethanol and acetic acid, or physical agents like radiofrequency or microwave, which induce thermal injury to the nodules. The limitation of these treatments is linked to the lesion’s size, 3 cm being the ideal cut-off limit. Survival rates following percutaneous treatment are similar to surgical resection (5-year survival about 40%, but when nodules <3 cm are considered, the 4-year survival reaches >70% for RFTA) [6]. Alcohol injection and radiofrequency are equally effective for tumors <2 cm, but the necrotic effect of radiofrequency is more predictable in all tumor sizes and its efficacy is clearly superior to that of alcohol injection in larger tumors. For non-surgical patients with large multifocal HCC who do not present vascular invasion or extrahepatic spread, BCLC and AASLD guidelines recommend TACE as first-line non-curative therapy. Recently, meta-analysis studies have shown a significant survival benefit compared with palliation. Patients who benefit better from this treatment are those with CP class A; CP class C patients and patients with a very poor life expectancy should not be treated [7] or should only receive symptomatic treatment.
References


