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Review Article

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Updates in the Management of Hepatocellular Carcinoma

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Abstract

Hepatocellular carcinoma (HCC) is one of the most common cancers worldwide. It forms about 7% of all cancers and is considered to be the third cause of cancer related deaths. East Asia is considered the most affected part. HCC is potentially curable with high incidence of mortality. Liver cirrhosis (due to hepatitis B, C, alcoholic related cirrhosis, and metabolic related disorders) is considered the main risk factor. Proper multidisciplinary teams are needed for proper management. The lines of treatment include liver resection and liver transplantation. Removal of the tumor with safety margin is considered the only way for recovery. Whenever surgery or transplantation is not achievable, local ablative therapies will be of benefit. These local modalities include radiofrequency ablation, radioembolisation, chemoembolisation, percutaneous ethanol ablation, and intrahepatic radiotherapy. They are able to prolong survival although they are of palliative nature. Systemic measures include chemotherapy, immunologic, hormonal therapies and molecular targeted therapies (Sorafenib). Other strategies include down staging and bridging that can improve the survival in patients with HCC on the waiting list waiting for liver transplantation.

Keywords

Hepatocellular carcinoma; Management; Liver transplantation; Liver resection; Loco regional ablative therapy; Systemic therapy

Introduction

Hepatocellular carcinoma (HCC) is one of the major health problems. It is the sixth most common cancer worldwide. It is considered the third cause of cancer related death [1]. Liver cirrhosis is the most common risk factor including hepatitis B, hepatitis C and alcohol related hepatitis [2].

Early cancer detection

Screening stable patients with cirrhosis aims for early detection of HCC in an early, asymptomatic stage. The most commonly used tests are serum α-fetoprotein (AFP) level and ultrasonography. The sensitivity of AFP (20 ng/Ml or above) in diagnosis of HCC ranges from 39% to 64% and the specificity ranges from 76% to 91% [3,4]. Ultrasound has high sensitivity and specificity rates for diagnosis of HCC ranging between 78% and 94%, [4] but for HCC nodules of less than 2 cm in diameter; cirrhotic patients these rates decreases to be less than 50%. Regenerative nodules, [5] focal fatty changes and dysplastic nodules have similar features like small HCCs.

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When ultrasound suspects HCC, contrast-enhanced computed tomography (CT) is the most appropriate test for confirming the diagnosis radiologically [6] CT is more sensitive than ultrasound in detecting multicentricity. Hepatic angiography combined with CT (angio-CT) can detect small foci of HCC. These foci can be identified during the arterial phase of the exam before portal venous delivery of contrast enhances the liver parenchyma [7]. Magnetic resonance imaging (MRI) can detect tumors less than 2 cm in diameter in 81% of cases [8]. CT with iodized oil (lipoidal CT) depends on the tumor's uptake and retention of iodinated oil after intra-arterial injection. Lipoidal CT has the ability to identify HCCs less than 1 cm in diameter in up to 83% of cases [9]. Preoperative imaging can miss multifocal lesions, satellite nodules, and vascular invasion.

Needle biopsy to prove the diagnosis is controversial especially when a lesion has typical radiological features of HCC is discovered. If a biopsy is necessary, a core sample will be appropriate specimen. Fine-needle aspiration should be avoided. A chest x-ray and CT of the chest should be performed as a part of the workup because the lungs are common sites of spread

Tumor staging

For almost all types of cancer, the tumor size, the presence of multiple foci, local vascular and/or lymphatic invasion and distant spread carry prognostic significance. In HCC patients, large, multiple, invasive cancers and those with distant spread carry poor prognosis [10,11]. Different staging systems are used to stage and manage patients with HCC. Each one has its advantages as well as some related defects [12]. The aim of these clinical staging systems is to assess patients and to help in making therapeutic decisions. To estimate the progress of patients with HCC properly, we should assess both liver function and tumor related factors; however, staging systems that include both these features had little analysis. In fact, the well-known systems for staging as International Union against Cancer (UICC) and American Joint Committee on Cancer (AJCC) staging system criteria do not define the relative prognostic weight of variables, in terms of residual liver function [13-15].

The prognostic assessment and choice of treatment in HCC patients are very important, and highly complicated, compared to any other carcinomas arising in other organs. This complexity is specifically due to the strong relation between the HCC prognosis and both the grade of cancer spread (tumor staging), and the grade of residual liver function (liver disease stage) [16-21].

The Tumor node metastasis (TNM) staging system is the most detailed staging system for tumor characteristics, and has been widely applied to all common cancers [22,23]. In this system, tumor characteristics are defined on the basis of the primary tumor (T) which describes size, number, distribution in the liver, the presence or absence of vascular invasion; (N) describes the presence or absence of node involvement; and (M) describes the presence or absence of distant metastases.

The TNM staging system and liver damage grade have been commonly used in Japan, based on the general rules for the clinical and pathological study of primary liver cancer of the Liver Cancer Study Group of Japan (LCSGJ) [24,25]. These classifications are very useful

in determination of the residual liver function and cancer spread, separately. However, this independent classification is not useful in terms of predicting the prognosis or in terms of determination of the suitability of a given therapeutic strategy for a given patient with HCC, because it has 12 subgroups (three liver disease stages times four tumor stages), which complicates the life expectancy assessment or the determination of the treatment strategy [26,27].

The current classifications most commonly used for HCC are the Child-Pugh score [28] TNM classification, and liver damage grade based on the General rules for the clinical and pathological study of primary liver cancer, of the LCSGJ [25]. Each classification has its own limitations. The Child-Pugh score and liver damage grade are not suitable for staging tumor spread. They consider only features related to liver function and do not include cancer parameters. The TNM classification includes only features related to tumor spread and does not include liver function parameters. The TNM, which is widely used for hepatic resection or transplantation, has been found to be inadequate by many investigators over the past few years [19,20,29].

The Okuda classification [16] includes both tumor parameters and liver function factors. The Okuda staging system is the first known staging system for HCC, with wide use in Japan and Eastern countries. It is the most common system used for staging and predicting the prognosis of patients with cirrhosis and HCC, according for both liver functions and tumor extent (more or less than 50% of liver involved) [16]. It is much suitable for patients with advanced HCC and who are not usually fit for any intervention maneuvers. However, it is now a bit outdated, because it does not include important tumor factors, such as whether the tumor is unifocal, multifocal, or diffuse; or whether there is vascular invasion; or whether the tumor is less than 2 cm in diameter; all of which factors have prognostic significance in early phase HCC.

The Barcelona Clinic Liver Cancer (BCLC) staging is a newly reported clinical staging system for HCC [30]. It is one of the most accepted and widely used systems. It was developed after retrospective analysis of several studies for several HCC stages [30]. This classification includes; performance status, single or multifocal tumor, vascular invasion, portal hypertension, Okuda stage, and Child-Pugh classification. Stage A was categorized as early-stage HCC (those patients who would benefit from curative therapies with 50%-70% 5-year survival rate), stage B as intermediate-stage HCC (50% survival rate at 3-years if untreated), stage C as advanced HCC (50% survival rate at 6 months), stage D as end stage HCC (50% survival rate of less than 3 months who should receive symptomatic treatment). Those in stage B or C should be assessed for palliation [30]. It is the most commonly used staging system in Europe and it has been used by the European Association for the Study of the Liver (EASL) and the American Association for the Study of Liver Diseases (AASLD) [31]. The limitation in this staging system is that it includes subjective evaluation factors such as performance status.

Cancer of the Liver Italian Program (CLIP) group staging system: a newer prognostic staging system was proposed by the CLIP group in 1998 that accounts for both liver function and tumor characteristics relevant to prognostic assessment for patients with HCC [32]. The score is easily computed and includes Child-Pugh stage, tumor morphology and extent, presence of portal vein thrombosis, and serum level of AFP. The CLIP scoring system was useful for treatment planning by improving the baseline prognostic evaluation of patients with HCC. It could accurately identify patients with different prognosis, particularly in the early phases of HCC, thus representing a useful tool in the management of patients with HCC. The CLIP group stratified the patients into seven groups according to prognostic indicators, but actually they evaluated only six groups, by placing score 5 and score 6 together into one group [32]. Furthermore, in the subsequent study, they reduced the number of strata to five, i.e., CLIP 0, 1, 2, 3, 4-6 (in fact four, considering that CLIP 2 and 3 have almost identical figures [33]. Even the outcome of the best prognostic subgroup in the CLIP system (score 0) exhibits a moderate 50% survival at 3 years, regardless of the treatment applied, which is extremely low. Many following studies validated this system and proved its superiority and accuracy compared to systems like Okuda or TNM staging systems [34], with specific advantage as a prognostic module even more than BCLC and the Japan Integrated Scoring (JIS) system [35].

The JIS score, new prognostic staging system, based on LCSGJ criteria. It combines the Child-Pugh grade and the TNM stage. Each patient with a Child-Pugh classification of A, B, and C was allocated scores of 0, 1, and 2, respectively. Based on the TNM staging of the LCSGJ, stage I (fulfilling the following three conditions: solitary, < 2 cm, no vessel invasion), stage II (fulfilling two of the three conditions), stage III (fulfilling one of the three conditions), and stage IV (fulfilling none of the three conditions) were allocated scores of 0, 1, 2, and 3, respectively. The summation of the tumor staging score and the Child-Pugh classification score was defined as the JIS [36]. JIS score, based on LCSGJ criteria, is currently the best prognostic system, to stage patients with HCC, in terms of including both tumor stage and liver disease stage. It is simple, easily obtained, and objective, can be used in routine clinical practice.[36] Now, this score is used only for local Japanese guidelines [37].

Group d' Etude et De Traitement du Carcinome Hepatocellulaire (GRETCH) score, French staging system, not widely used, included the performance status as one of its parameters [38].

Chinese University Prognostic Index (CUPI) system performed in Hong Kong, [39] depends on variables such as tumor extension (with TNM classification), liver profile and presence of symptoms at presentation. It is suitable for advanced rather than early ones [40].

Treatment

Early detection and accurate staging of HCC are very important as they determine the ability to offer the proper therapy. Many treatment options are available which depend on patient factors as performance status and tumor factors as size, location, number and extratumoral spread.

Treatment of HCC needs Multidisciplinary HCC team: HCC has various presentations. Also patients vary as candidates for wide variety of therapeutic options, with wide diverse in response to these therapies in clinical practice [41]. HCC has high variable biological behavior and frequent association with liver cirrhosis or chronic liver disease [42]. The Multidisciplinary team includes hepatologists, surgical oncologists, medical oncologists, transplant surgeons, diagnostic and interventional radiologists, pathologists, nurses and nurse practitioners [43].

Surgery

Surgery is the corner stone in HCC management. It is the best option for patients who are candidate for such treatment option [44]. Surgical approaches range from complete resection of small localized tumors to liver transplantation. Surgical resection is the most suitable

for solitary tumors in patients without cirrhosis, with 5 year survival rates of 41-74% [26,45-50].

In patients with cirrhosis or multiple tumors, resection may be not the most suitable option. Liver function status, presence of portal hypertension, or decompensated liver disease are factors to be considered before surgery. Surgery for large HCC carries high risk of tumor dissemination, and vascular invasion except in well circumscribed tumors [51].

The risk of recurrence after tumor resection reaches 70% at 5 years. De novo tumor development can occur following resection but most of HCC recurrences within 1-2 years after resection are secondary to dissemination from primary tumor. Repeat resection may not have benefit as most recurrences have multifocal presentation which makes transplantation or loco regional therapies more suitable [52]

The indication for liver transplantation (LT) in patients with HCC has been much debated. Numerous studies showed equal or favorable outcomes of LT for HCC [53]. Whenever transplantation is contemplated for the treatment of HCC, an attempt should be made to characterize the primary growth as accurately as possible and to detect or exclude extra hepatic spread. The presence of any demonstrable cancer outside the liver is the single most important contraindication to transplantation for HCC. There is no consensus on the size of an HCC that should be regarded as an absolute contraindication to transplantation, but many centers use an upper limit of 5 cm.

In the Milan study, tumors 5 cm or less in diameter in patients with a single HCC or no more than 3 tumor nodules with each one 3 cm or less in diameter were associated with an improved survival rate (85%) and a recurrence-free survival rate (92%) [54]. The Milan criteria have been accepted as selection criteria for allocation of cadaveric liver to patients with small, unresectable HCC [20,55,56]. When adhere to these criteria, 5 year survival rates after transplantation range from 70-80%, and tumor recurrence rates are approximately 10% [20,46,55,57,58]. Several studies have investigated the effect of expanding Milan criteria with some centers reported promising results with survival rates and recurrence free rates similar to those restrict to Milan criteria [56,59-63]. The expansion to University of California San Francisco (UCSF) criteria (single nodule ≤ 6.5 cm or 2-3 nodules ≤ 4.5 cm and total tumor diameter ≤ 8 cm) which involves around 5-10% of all transplant enlisted patients [63]. Recently, attempts of down staging for patients exceeding the Milan criteria has been done by performing loco regional therapy in order to decrease the tumor burden so that the patient can meet the Milan criteria [64,65]. Successful down staging should include tumor size, and number of viable tumors and AFP concentrations before and after down staging, then a minimum observation period of 3 months is recommended before liver transplantation [66]. Bridging is another strategy for patients whose HCC is at risk or shows signs of progression while waiting for a graft for 6 months or longer. This strategy is appropriate for patients with United Network for Organ Sharing (UNOS) T2 lesions (one nodule 2-5 cm or three or fewer nodules each ≤ 3 cm) [19,20,64].

In case of living donor liver transplantation, the recipients who have relatively large and/or numerous tumors with poor liver function with no vascular invasion, are not excluded despite not fulfilling the Milan criteria (graft donation only depends on the donor's intention) [67,68].

Non-surgical invasive therapies

Patients who are not suitable for surgery are amenable for non-surgical therapies [69]. Local ablation techniques are used mainly for patients unfit for surgery. These techniques are safe and effective as primary treatment of localized small tumors in certain sites or as a bridge to transplantation. These modalities can be performed through percutaneous approach or laparoscopically. They destroy tumor cells either directly by exposing the tumor to toxic substances e.g. ethanol or by modifying the temperature. These techniques include percutaneous ethanol injection (PEI), radiofrequency ablation (RFA), microwave ablation, cryoablation, laser-induced thermotherapy, high intensity focused ultrasound and irreversible electroporation [70].

The first used technique was PEI which induces necrosis as a result of cellular dehydration and protein denaturation. The use of temperature in ablation appeared later, using either heating as in RFA, microwave ablation and laser ablation or direct tumor freezing [69]. RFA and PEI are the most commonly used ablative techniques. The estimated 5 year survival in patients with early HCC was 47-53% [71]. Other studies showed efficacy in both techniques in achieving tumor necrosis in 90-100% with tumors less than 2 cm [72-75]. Recently, RFA is the most commonly used local ablative technique and largely replaced PEI with better results regarding survival and recurrence with fewer treatment sessions [76]. It depends on energy production that induces coagulative necrosis with safety margin.

Transarterial chemoembolisation (TACE)

It is recommended as the first line, non-curative treatment, among patients with large multifocal HCC or patients whose tumor characteristics are not appropriate for surgery or ablation without vascular invasion or extra hepatic spread [77,78]. The well characterized angiogenic activity of HCC was the rational of TACE use. It depends on the intra-arterial infusion of cytotoxic chemotherapeutic agent emulsified with lipiodol followed by embolization of the feeding vessels through a trans-arterial catheter [79].

When liver transplantation became an option for the management of HCC, TACE has been advocated with the aim of causing necrosis of the primary tumor and diminishing the likelihood of further growth or metastasis between the time of treatment and time of transplantation. The selective route minimizes systemic toxicity, delivers a high dose of the drug directly to the tumor, and maintains a high concentration of the drug within the tumor [80].

Radioembolisation

Is the delivery of radioactive substances such as Iodine-131 labeled Lipiodol [81] or microspheres containing Yttrium-90 [82]. The injected microspheres will reach the tumor area with selective production of high energy and low penetration radiation. This has the advantage of the ability to perform it safely in patients with portal vein thrombosis owing to the minimally embolic effect of 90Y microspheres [83].

Systemic therapies

Studies failed to demonstrate an impact of cytotoxic chemotherapy on overall unresectable HCC survival rates [84]. However, newer agents that utilize antiangiogenic modalities proved promising results. Sorafenib, the first successful targeted drug, is considered the standard systemic therapy for HCC [85]. It is an orally administered multikinase inhibitor drug with antiproliferative and antiangiogenic activity [86]. Its main indication is patients with preserved liver function (Child-Pugh A class) [87] who have advanced tumors (BCLC C) [30]. It is also indicated for tumors progressing on loco-regional therapies [88]. Current guidelines from the AASLD recommend

Sorafenib as a first-line therapy in patients with unresectable HCC who are not appropriate candidates for percutaneous ablation or TACE but who maintained preserved liver function. Sorafenib HCC Assessment Randomized Protocol (SHARP) trial is a large randomized phase III study. This trial succeeded to record an increase in the median overall survival from 7.9 months in placebo group to 10.7 months in the Sorafenib group [85].

Additional antiangiogenic agents are also being investigated. Bevacizumab, a human monoclonal antibody directed against vascular endothelial growth factor (VEGF), has been used in phase II trials either as single agent [89] or in combination with other cytotoxic drugs. It did not move to phase III trials may be due to possible sever hemorrhagic events. Erlotinib, an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor, has demonstrated encouraging results in early studies and further studies are still in progress [90,91]. Everolimus, (P13K/PTEN/Akt/m TOR Target) showed a 44% disease control rate allowing it to pass to phase III trial as a second line treatment after Sorafenib failure or intolerance [92].

These novel agents, combined with surgical resection, transplantation and/or ablation may offer the most potential in an adjuvant or neoadjuvant fashion [93].

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