Nutritional therapy for hepatocellular carcinoma

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Abstract

Hepatocellular carcinoma (HCC) is the most frequent primary liver cancer and presents together with cirrhosis in most cases. In addition to commonly recognized risk factors for HCC development, such as hepatitis B virus/hepatitis C virus infection, age and alcohol/tobacco consumption, there are nutritional risk factors also related to HCC development including high intake of saturated fats derived from red meat, type of cooking (generation of heterocyclic amines) and contamination of foods with aflatoxins. On the contrary, protective nutritional factors include diets rich in fiber, fruits and vegetables, n-3 polyunsaturated fatty acids and coffee. While the patient is being evaluated for staging and treatment of HCC, special attention should be paid to nutritional support, including proper nutritional assessment and therapy by a multidisciplinary team. It must be considered that these patients usually develop HCC on top of long-lasting cirrhosis, and therefore they could present with severe malnutrition. Cirrhosis-related complications should be properly addressed and considered for nutritional care. In addition to traditional methods, functional testing, phase angle and computed tomography scan derived skeletal muscle index-L3 are among the most useful tools for nutritional assessment. Nutritional therapy should be centered on providing enough energy and protein to manage the increased requirements of both cirrhosis and cancer. Supplementation with branched-chain amino acids is also recommended as it improves response to treatment, nutritional status and survival, and finally physical exercise must be encouraged

and adapted to individual needs.

Key Words: Sarcopenia; Liver; Cancer; Diet; Branched-chain amino acids; Nutrition

Core Tip: Hepatocellular carcinoma is often found in patients with cirrhosis; nutritional management for both conditions can be challenging due to increased energy requirements and increased liver-related complications. Nutritional support must include sufficient energy and proteins to overcome the highly catabolic state derived from the two conditions. Branched-chain amino acids are recommended in both cirrhosis and hepatocellular carcinoma as they can improve muscle mass, body protein, response to treatment and quality of life. Finally, an adequate and feasible exercise program should be provided as a part of the nutritional plan, aiming to improve the overall status.

INTRODUCTION

Liver cancer is the sixth most common cancer and the second leading cause of cancer-related deaths globally; hepatocellular carcinoma (HCC) represents about 70%-90% of primary liver cancers and constitutes a major public health problem worldwide[1-3].

HCC is an especially challenging clinical scenario for people involved with its care; this is particularly difficult for dietitians and specialists involved in the nutritional care of these patients due to two factors: the accompanying cirrhosis in most of the cases (and therefore the cirrhosis-specific needs) and the nutritional requirements derived from cancer itself.

The first part of this review includes general information related to HCC, aimed to provide the basic knowledge of the disease to screen patients and recognize them in clinical practice. The second part of the review includes the nutritional approach, clinical relevance of nutritional status and the best options for nutritional treatment.

EPIDEMIOLOGY AND RISK FACTORS

Liver cancer constitutes the fifth most frequent cancer in men and the seventh most frequent in women, according to age-standardized incidence rates[3]. It is more common in men than in women, with a ratio of 2.4:1. Incidence of HCC varies between geographic regions and ethnic groups depending on the prevalence of risk factors, although it increases progressively with age in all populations, reaching a peak during the seventh decade of life[4].

Emerging evidence indicates that the etiology in many cases of HCC is multifactorial, involving infections, comorbid conditions, and environmental exposure. In most cases, HCC arises in the setting of cirrhosis; in fact, the annual incidence of HCC arising from cirrhosis ranges from 2% to 5%[5]. The most common risk factors for HCC worldwide include hepatitis B virus (HBV), hepatitis C virus (HCV) and aflatoxin B_1 exposure[6-8].

From a public health perspective, active HCV and HBV infections continue to drive most of the global burden of cirrhosis and subsequent HCC[9]. HCV carriers have 15 to 20 times higher risk of developing HCC than non-carriers. In people infected with HBV, exposure to aflatoxin is associated with a risk of HCC up to 30 times greater than in those exposed to aflatoxin alone[10]. In addition, the risk increases in patients with HBV/human immunodeficiency virus coinfection, in males and in the elderly. In the same way, the time of infection also seems to increase the risk of developing cancer, as

does excessive alcohol consumption and active smoking[6].

It is likely that in the next few years, HCV/HBV as the primary cause of HCC will decrease significantly due to the availability of HCV curative treatment and HBV vaccines, whereas metabolic-associated fatty liver disease will become the major contributor to the global burden of HCC. Regarding this, up to 70% of patients with type 2 diabetes mellitus have metabolic-associated fatty liver disease, and in this context the probability of developing HCC doubles in patients with both diseases[2]. Additionally, there is a higher predisposition to cancer among carriers of the PNPLA3 rs378409 risk allele and the LEP rs7799039 polymorphism[11].

DIETARY INVOLVEMENT IN HCC DEVELOPMENT

Although there are many factors involved in HCC development, there is a role of dietary factors that can help prevent its development or increase its risk. Figure 1 summarizes this data.

Nutritional risk factors

Many studies have pointed to the possibility that specific components or nutrients in the diet are associated with an increased risk of different types of cancer, including HCC.

The main dietary risk factor for the development of HCC is the contamination of food with aflatoxins. Aflatoxins are a group of mycotoxins produced by the fungi *Aspergillus flavus* and *Aspergillus parasiticus* that are produced by improper storage of certain foods and constitute a risk factor that plays a causal role in 4.6%-28.2% of all worldwide HCC cases.

Aflatoxins can be found in products such as corn, wheat, peanuts, rice, sesame, sunflower seed, cottonseed and many spices; the presence of aflatoxins in these foods can be due to aspergillus infection during crop growth or due to an improper transport or storage where they are exposed to warm and humid conditions. Even animals fed with contaminated foods can pass aflatoxins into eggs and dairy products.

Another dietary factor associated with the development of HCC is excessive consumption of saturated fats especially those derived from red meat. The mechanisms are believed to be the generation of reactive oxygen species when iron is reduced in the diet (Fenton reaction) and through the generation of heterocyclic amines when meat is cooked at high temperatures. A prospective cohort study found that red meat intake was associated with an increased risk of mortality from liver disease and the incidence of HCC (hazard ratio: 1.74, 95% confidence interval: 1.16-2.61, 14.9 *vs* 5.7 cases/100000 person-years)[12]. Diets rich in red meat also correlate with circulating markers of inflammation and endothelial dysfunction, potentially having a negative influence in patients with both cirrhosis and HCC[13].

Finally, obesity, particularly abdominal obesity, also confers an increased risk of developing HCC according to various epidemiological studies. This risk seems to be related to the adipose tissue production of adipokines (leptin, adiponectin and resistin)[14]. Interestingly, the serum levels of leptin are elevated in patients with HCC, which points to the role of this adipokine as a promoter of HCC in obese patients.

Nutritional protective factors

In contrast with other types of cancer, relatively few studies have investigated the protective effect of diet on HCC.

It has been found that the consumption of fish rich in n-3 polyunsaturated fatty acids or supplementation with n-3 polyunsaturated fatty acids seems to protect against the development of HCC, even among subjects with HBV and/or HCV infection[15]. Fatty acids could exert anticancer effects through their ability to induce apoptosis of cells, regulate cell cycle and manipulate the production of eicosanoids[16].

Similarly, evidence indicates that polyphenols, found mainly in fresh fruits and vegetables, target angiogenesis and metastasis in HCC through regulation of multiple intracellular signals and finally reducing the risk of HCC[17,18].

Another important source of polyphenols is coffee, and in fact, the protective role of coffee in liver diseases has been well documented. Coffee is a complex mix of different chemicals including antioxidants and mutagenic and antimutagenic compounds; the mechanisms of action are unclear but may involve modification of cysteine residues in proteins that play important roles in liver carcinogenesis[19]. Interestingly, increased consumption of more than two cups of caffeinated coffee, and to a lesser extent decaffeinated coffee, is associated with a reduced risk of HCC, even in pre-existing
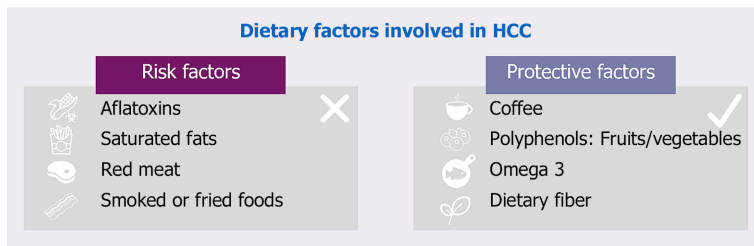
Figure 1 Dietary factors associated with risk and protection for the development of hepatocellular carcinoma. HCC: Hepatocellular carcinoma.

liver disease[20].

On the other hand, diets with a high fiber content could reduce the risk of HCC by reducing subjective appetite and energy intake, contributing to the maintenance of healthy body weight in addition to exerting a beneficial effect on postprandial glucose levels and lipid profile[21,22]. Other protective mechanisms include binding to bile acids, with inhibition of their transformation to secondary bile acids, increasing hydration of the fecal bolus, diluting possible carcinogens, modification of the colonic flora with inhibition of bacterial enzymes responsible for the formation of carcinogens and decrease in intestinal transit time with less contact time between carcinogens and the intestinal wall[22].

CLINICAL MANIFESTATIONS AND DIAGNOSIS

HCC usually manifests with nonspecific symptoms. Some patients are asymptomatic at the time of diagnosis, but in advanced stages, clinical findings may include right upper quadrant abdominal pain and symptoms of malignant disease such as nausea, anorexia, malaise, fatigue and weight loss. Patients with unrecognized cirrhosis or known compensated cirrhosis may also present with liver decompensation including ascites, jaundice, variceal bleeding, portal vein invasion and thrombosis[1,23].

The diagnosis of HCC is mainly based on imaging studies and laboratory tests. In most cases, assuming tumor meets imaging criteria in patient at increased risk, biopsy is rarely needed. Triple-phase contrast enhanced computerized tomography (CT) is a sensitive and specific tool for identifying liver lesions larger than 1 cm[24,25]. The classic radiological finding is arterial enhancement with early washout in the portal phase. Other diagnostic options are gadolinium or liver-specific contrast agents for enhanced magnetic resonance imaging and contrast ultrasound (higher diagnostic performance than conventional ultrasound). In 2011, the Liver Imaging Reporting and Data System was introduced to standardize the reporting and collection of CT and magnetic resonance imaging findings for HCC[26]. The Liver Imaging Reporting and Data System classifies liver lesions into five categories based on size, threshold growth and enhancement patterns (enhancing capsule and washout). It is important to consider liver biopsy in those patients without cirrhosis, small lesions and probably malignant lesions (Liver Imaging Reporting and Data System 4).

Alpha-fetoprotein is elevated above 20 ng/mL in more than 70% of patients with HCC. However, its specificity is quite poor since high levels are associated with inflammatory states, such as viral hepatitis and tobacco use, although levels > 200 ng/mL have a high positive predictive value of HCC in patients with cirrhosis[1].

STAGING AND TREATMENT

Staging

Staging assessment is crucial to establish prognosis and treatment of patients with HCC. This evaluation should include tumor stage, severity of the underlying liver disease and performance status. Several staging systems have been developed for prognosis; the most widely used is the Barcelona Clinic Liver Cancer (BCLC) staging system is recommended both for prognostic prediction and treatment allocation and remains as the most validated and reliable system used widely. It is endorsed in several international clinical practice guidelines[27]. BCLC staging system classify patients in five stages. This classification categorizes patients into early HCC (stage 0 and A), intermediate HCC (stage B), advanced HCC (stage C) and end-stage HCC

(stage D)[27].

Treatment

The goal of treatment in patients with HCC is to increase survival with the best possible quality of life, and therefore treatment decisions revolve around what is worth doing and should be agreed upon by a multidisciplinary team.

Surgical resection should be offered to patients with a single lesion and a non-cirrhotic liver or with cirrhosis and a hepatic venous pressure gradient lower than 10 mmHg without evidence of hepatic decompensation[28].

There are different therapeutic tools that are tumor-directed. One of these is transar-terial chemoembolization, which uses injection of a chemotherapeutic agents into the tumor-feeding hepatic artery, followed by obstruction of this artery, reducing tumor burden and delaying progression. Also, it is particularly useful in patients on the transplant list if the waiting time is expected to be more than 6 months[29]. TACE is the first-line non-curative therapy for patients with multifocal HCC or lesions greater than 5 cm that does not have vascular invasion or extrahepatic spread. On the other hand, percutaneous ethanol injection is minimally invasive, safe, and associated with a low cost. Radiofrequency ablation is another tumor-directed treatment that uses a percutaneous or in situ heat-generating probe to destroy tumor cells and has a more predictable effect in tumors larger than 2 cm[1].

In patients with advanced HCC, monotherapy with sorafenib, a tyrosine kinase inhibitor, has a small but significant survival benefit compared to supportive care[23]. Phase III randomized controlled trials with lenvatinib as first-line therapy and regorafenib, cabozantinib and ramucirumab as second-line therapy, after disease progression with sorafenib, have shown good results. Regorafenib is now approved by the Food and Drug Administration in this setting. Immunotherapy with the programmed cell death protein 1 checkpoint inhibitor, nivolumab, is in phase II trials with accelerated Food and Drug Administration approval, while other kinase inhibitors (sunitinib, brivanib and erlotinib) showed no benefit in mortality in unresectable HCC[30].

Liver transplantation is a highly effective therapeutic option for unresectable early-stage HCC, especially in patients with underlying liver cirrhosis; it offers the best treatment of both the chronic liver disease and the tumor and is associated with excellent long-term survival rates for HCC within certain criteria[31,32]. In order to achieve an optimal distribution of the limited number of available liver allografts for the patients on the waiting list, it is important to identify the patients who benefit most from liver transplantation with an acceptably good prognosis[33].

Thus, in 1996, a prospective cohort study defined restrictive selection criteria that led to superior survival for transplant patients with HCC. In this study, transplant eligibility criteria included: a single lesion ≤ 5 cm or 3 or fewer lesions all < 3 cm and no evidence of macrovascular invasion, lymph node involvement or extrahepatic metastasis[33]. Since then, these selection criteria are known as the Milan criteria and represent the criterion standard in transplant programs to select and list patients with HCC for liver transplantation in many centers[34].

Expanded criteria beyond the Milan criteria (*e.g.*, UCSF criteria and up-to-7 criteria) and the use of downstaging therapies to meet Milan criteria have resulted in similar post-transplant outcomes. Of note, these criteria focus mainly on tumor volume, and do not factor in tumor biology[33].

It is important that specialists in nutrition involved in the care of HCC patients know these modalities of treatment because they will add even more "nutritional stress" into a patient with two conditions (both cirrhosis and cancer) with a high risk of malnutrition. Therefore, additional nutritional care should be provided after surgery, either liver transplantation or resection, given the increase in metabolic demand. On the other hand, side effects such as nausea, hyporexia and pain can be present during the use of some of the above-mentioned therapies (systemic therapy, TACE, radiofrequency ablation), limiting usual nutritional support.

NUTRITIONAL APPROACH IN PATIENTS WITH CIRRHOSIS AND HCC

Nutritional assessment

Nutritional assessment is of great importance in patients with cirrhosis and HCC, the goal is to establish a baseline body composition assessment and continue with frequent follow-ups to monitor the response to nutritional therapy. It is important to consider the fact that patients with previous liver disease have many complications

that make nutritional assessment very complex. First, the decrease of hepatocyte synthesis of proteins such as albumin, make these common biomarkers unreliable for nutritional diagnosis. Second, the presence of complications such as ascites/edema and hepatic encephalopathy also limit the use of other methods. Traditional markers, such as body weight, body mass index and even bioelectrical impedance (for prediction of fat mass, fat free mass and skeletal muscle mass) are directly influenced by fluid overload; while hepatic encephalopathy hampers the use of functional testing such as handgrip-strength, six-minute walk test and frailty assessment. All these issues must be acknowledged in order to select the best and most reliable tool for nutritional assessment[35].

There are simple anthropometric methods, such as mid-arm muscle circumference, mid-arm area and triceps skinfold thickness measurement, that reflect muscle and fat content. They have been widely used and validated and are easy to implement in clinical practice[36].

In terms of functional testing, it can be applied when hepatic encephalopathy is not present. Handgrip strength is a widely used method that measures muscle strength typically with a hand-held dynamometer[37]. Recently, liver frailty index was developed and has been validated in patients with cirrhosis. It also includes handgrip strength and adds two more tests: time to complete five chair stands and time in three balance positions. These tests are inexpensive and easy to perform and can be used in outpatient clinics[38].

Another useful nutritional marker is phase angle (PhA) derived from bioelectrical impedance. It reflects the integrity of cell membranes and tissue homeostasis as well as muscle integrity[39]. Several studies have reported PhA as a clinically useful nutritional marker, predicting complications and mortality both in elderly people and in cirrhosis, where a PhA value < 4.9 is associated with higher risk of hepatic encephalopathy and decreased survival[40-42]. Furthermore, PhA has been widely used and validated as a nutritional marker associated to survival in different types of cancer [43]. Therefore, it is reasonable to use PhA in patients with cirrhosis and HCC, as has been shown in a small study including 51 patients with HCC, where a PhA < 4.8 was associated with higher mortality[44]. PhA has been recently validated against CT scan as a marker of sarcopenia in cirrhosis, where values of PhA < 5.4 in females and < 5.6 in males are diagnostic of sarcopenia[45]; this is a marker derived from a portable device and can be used in all settings, outpatients, hospitalized patients and even critically ill patients as it does not require active participation. Thus, this is a reliable tool for the sequential assessment of patients with cirrhosis requiring multiple evaluations to monitor response to nutritional treatment.

Finally, skeletal muscle index-L3 derived from CT scan is considered the gold standard for body composition assessment. It quantifies the total muscle area at the third lumbar vertebra, and it is normalized for the patient's height. It is a very accurate method, although it remains difficult to include in daily clinical practice; however, patients with HCC require several imaging studies, including CT and/or magnetic resonance imaging for diagnosis and monitoring response to treatment. Thus, these already available images can also be used to evaluate body composition. The additional advantage of this method is allowing the detection of ascites and even the presence of myosteatosis[46]. For practical reasons, including costs, patient comfort and availability, these methods are not suitable for serial monitoring.

Regardless of the method of choice (based on expertise with the method, costs, and availability) for nutritional assessment, decreased skeletal muscle mass is associated with a worse prognosis, including lower response to treatment and lower survival; a summary of the studies addressing this topic is found in Table 1. All patients with HCC should be evaluated and monitored by nutrition specialists specialized in liver disease due to the enormous impact that nutritional status has on the prognosis of patients. It is important that these patients are referred early to avoid the progression of malnutrition.

NUTRITIONAL THERAPY

After thorough nutritional assessment, dietary advice and tailored nutritional therapy must be indicated. Figure 2 includes a summary of dietary recommendations depending on the BCLC stage.

Nutritional interventions must be individualized, considering many aspects such as the presence and etiology of cirrhosis, the stage of the underlying liver disease and the stage HCC, the presence of malnutrition and its degree, comorbidities as well as the

Table 1 Studies evaluating the association of nutritional status and prognosis in patients with hepatocellular carcinoma

Ref.	Population	Method of nutritional assessment and malnutrition prevalence	Outcomes
Faron *et al* [56], 2020	58 patients with HCC receiving Yttrium-radioembolization. (78% with cirrhosis). BCLC Stage *n* (%): A: 1 (2.0); B: 13 (25.5); C: 23 (45.1)	MRI derived fat-free muscle. Cut-off values: < 3582 mm^2 in men. < 2301 mm^2 in women. 50%	Patients with low FFMA showed significantly reduced overall survival (197 d *vs* 294 d, P = 0.024). Low FFMA (HR: 2.675, P = 0.011), estimated liver tumor burden (HR: 4.058, P = 0.001) and Eastern Cooperative Oncology Group performance status (1.763, P = 0.009) were independent predictors of OS on multivariate analysis
Fujita *et al* [57], 2019	179 patients with HCC receiving TACE (100% with cirrhosis). TNM Stage *n* (%): I: 14 (7.8); II: 70 (39.1); III: 71 (39.7); IVA: 17 (9.5); IVB: 7 (3.9)	Psoas mass index. Cut-off values: < 6.0 cm^2/m^2 in men. < 3.4 cm^2/m^2 in women. 44.7%	There were no significant differences in OS between groups with low and normal psoas mass index. Multivariate analysis showed that change in PMI per month during the TACE period was significantly associated with poor overall survival (HR: 1.884, P = 0.001)
Kobayashi *et al* [58], 2018	102 patients with HCC and transcatheter intra-arterial therapies. (100% with cirrhosis). TNM Stage *n* (%): I: 11 (10.8); II: 22 (21.6); III: 46 (45.1); IV: 23 (22.5)	SMI-L3. Cut-off values: 42 cm^2/m^2 in men. 38 cm^2/m^2 in women. 30.4%	Univariate analysis using a Cox proportional hazards model revealed no significant association between SMI-L3 and OS rate (HR: 1.405, 95%CI: 0.861–2.293, P = 0.174). Multivariate analysis revealed that skeletal muscle loss (HR: 1.675, 95%CI: 1.031–2.721, P = 0.037), serum AFP ≥ 20 ng/mL, and maximum tumor diameter ≥ 30 mm were independently predictive of poor overall survival
Nishikawa *et al* [59], 2017	232 patients with HCC treated with sorafenib. (100% with cirrhosis). TNM Stage *n* (%): I: 1 (0.6); II: 18 (7.6); III: 79 (34.1); IVA: 46 (19.8); IVB: 88 (37.9)	SMI-L3. Cut-off values: 36.2 cm^2/m^2 in men. 29.6 cm^2/m^2 in women. 65.1%	The median overall survival time was 174 d in the sarcopenia group and 454 d in the non-sarcopenia group (P < 0.0001). The median PFS was 77 d in the sarcopenia group and 106 d in the non-sarcopenia group (P = 0.0131). Multivariate analysis identified sarcopenia to be an independent predictor of OS (hazard ratio, 0.365, P < 0.0001)
Schütte *et al* [44] 2015	51 patients with HCC (82.4% with cirrhosis). BCLC Stage *n* (%): A: 12 (23.5); B: 13 (25.5); C: 23 (45.1); D: 3 (5.9)	Mini nutritional assessment 0% (37.3% risk for malnutrition). Nutritional Risk Screening 33.4%. BIA derived PhA 23.5%	Patients with a PhA of up to 4.8 had a median survival of 298 d (95%CI 229-367 d) while patients with a PhA > 4.8 had a median survival of 399 d (95%CI 351-446, P = 0.026). Multivariate Cox regression confirmed the PhA at a cut-off of 4.8 in addition to BCLC stage to significantly influence survival of patients
Levolger *et al* [60], 2015	90 patients with HCC undergoing surgical resection or radiofrequency ablation. (50% with cirrhosis). BCLC Stage *n* (%): A: 15 (16.7); B: 30 (33.3); C: 36 (40.0); D: 9 (10.0)	SMI-L3. Cut-off values: 52.0 cm^2/m^2 in men. 39.5 cm^2/m^2 in women. 57.8%	Sarcopenic patients had a limited overall survival (median: 33 mo *vs* non-sarcopenic median: 105 mo, P = 0.002). Sarcopenia was an independent predictor for overall survival in multivariate Cox-regression analysis (HR: 3.756, P = 0.001), major complications (32.7% *vs* 13.2%, P = 0.033) and treatment-related mortality (17.3% *vs* 2.6%, P = 0.029) were more frequent in sarcopenic patient
Iritani *et al* [61], 2015	217 patients with HCC. (100% with cirrhosis). Tumor stage *n* (%) (according to the Liver Cancer Study Group of Japan): I: 52 (24.0); II: 71 (32.7); III: 66 (30.4); IV: 28 (12.9)	FFM. Cut-off values: < 37.0 kg. 45.6%. SMI-L3. Cut-off values: < 36.0 cm^2/m^2 in men. < 29.0 cm^2/m^2 in women. 11.1%	Multivariate analysis indicated that FFM (P = 0.0499), albumin level (P = 0.0398), and curability of the initial treatment (P = 0.0008) were independent prognostic factors. Sarcopenic patients showed a significantly lower overall survival than those without sarcopenia (P = 0.0043)
Harimoto *et al* [62], 2013	186 patients with curative resection for HCC. (53% with cirrhosis). TNM Stage *n* (%): I: 29 (15.6); II: 95 (51.1); III: 49 (26.3); IV: 13 (7.0)	SMI-L3. Cut-off values: < 43.75 cm^2/m^2 in men. < 41.10 cm^2/m^2 in women. 40.3%	In patients with and without sarcopenia, the 5 yr overall survival rate was 71.0% and 83.7%, respectively. The 5 yr recurrence-free survival rate was 13% and 33.2% respectively. Multivariable analysis revealed that reduced skeletal muscle mass was predictive of an unfavorable prognosis

AFP: Alpha-fetoprotein; BCLC: Barcelona Clinic Liver Cancer; BIA: Bioelectrical impedance analysis; CI: Confidence interval; FFM: Fat-free mass; FFMA: Fat-free muscle area; HCC: Carcinoma hepatocellular; HR: Hazard ratio; MRI: Magnetic resonance imaging; OS: Overall survival; PFS: Progression-free survival; PhA: Phase angle; PMI: Psoas mass index; SMI-L3: L3 skeletal muscle index; TACE: Transcatheter arterial chemoembolization; TNM stage: Classification of malignant tumors.

physical activity level of the patient. It is also important to consider surgical or radiological treatments to which the patient is subjected and to consider this level of physical stress in the calculation of the total energy expenditure.

Total energy expenditure mainly depends on the presence or absence of cirrhosis and malnutrition and can be calculated by indirect calorimetry or estimated by standardized formulas. Also rapid weight based formulas are available and suggested by the European Society for Clinical Nutrition and Metabolism guidelines[47].

Energy needs and protein requirements increase as the disease progresses. General recommendations from the European Society for Clinical Nutrition and Metabolism for liver disease and for cancer patients suggest 1.2-1.5g/kg/d of protein, and given the intrinsic hyper metabolism of cirrhosis, energy provision must be at least 30-40 kcals in early to advance stages of HCC and up to 45 kcals in terminal stages. To improve energy intake, frequent meals are recommended, and if energy intake is not
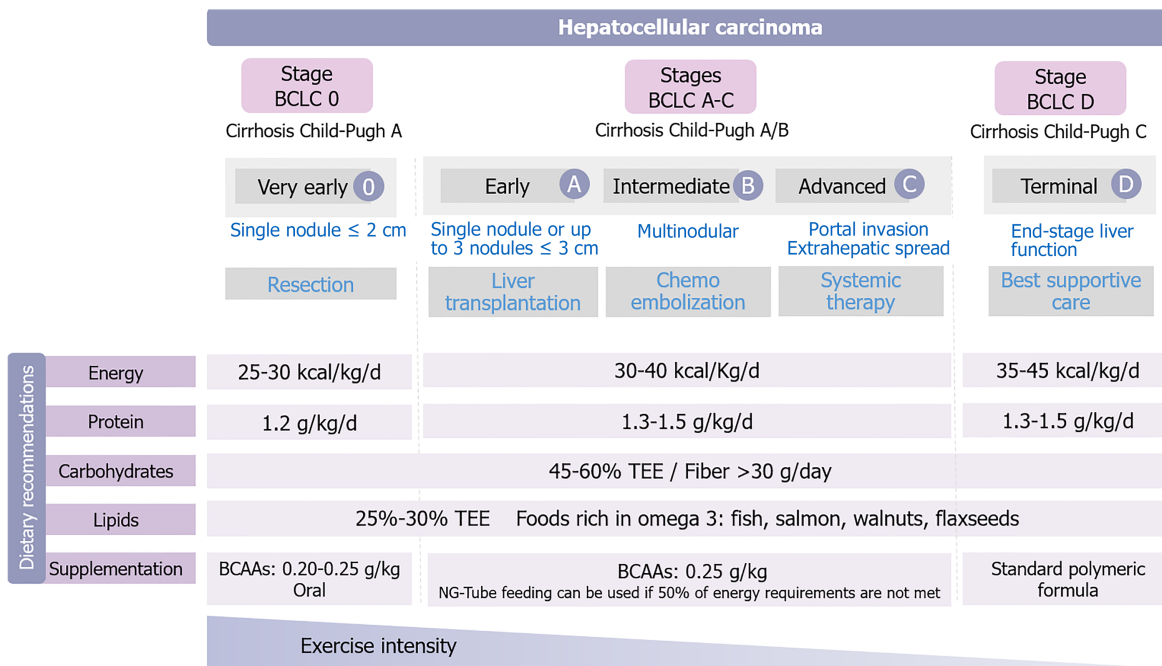
Figure 2 Nutritional therapy recommendations for hepatocellular carcinoma according to Barcelona Clinic Liver Cancer classification. BCAAs: Branched-chain amino acids; BCLC: Barcelona Clinic Liver Cancer; TEE: Total energy expenditure.

met orally, nasogastric tube feeding is advised, especially while on the waitlist for liver transplantation[47,48].

It is estimated that carbohydrates should contribute 45%-60% of the total daily energy expenditure, and complex carbohydrates must be included to get > 30 g of fiber. Once the protein and carbohydrate intake has been established, the rest of the total energy expenditure must be covered by lipids, paying special attention to meeting the needs for polyunsaturated fatty acids[48,49].

Finally, in patients with cirrhosis and HCC, supplementation with branched-chain amino acids (BCAAs), which include leucine, isoleucine and valine, is always recommended. BCAAs are the most widely studied type of supplement in HCC, and when given to these patients it has a beneficial effect in all stages of HCC, mainly in HCC stages 0 to C[47]. Preservation of liver function in patients with HCC is of great relevance, and in this context, there is evidence of the potential beneficial effect of BCAAs. On the one hand, they increase the efficiency of the treatment in HCC, by improving liver function and also increasing albumin when used from early stages, in addition to increasing the BCAA/L-tyrosine molar ratio[50]. Thus, early administration of BCAAs can improve outcomes after cancer therapy, even in the absence of encephalopathy and hypoproteinemia. Mainly, BCAA intake greater than 3 mo anticipates various benefits including prevention of a reduction in residual liver function caused by HCC treatment and prevention of recurrence after HCC treatment. Even BCAA granules have been reported to be effective in inhibiting early relapse after hepatectomy[51].

For unresectable HCC, it is common to perform TACE repeatedly, but it is necessary to pay attention to the liver function after this procedure. In this respect, the administration of BCAA granules prior to TACE inhibited reduction of serum albumin levels measured 3 mo and 6 mo after TACE and helped maintain residual liver function in patients with cirrhosis[51,52]. A summary of the evidence on BCAAs supplementation in HCC is found in Table 2.

It is important to consider that although BCLC D patients have a poor prognosis, and nutritional support does not improve survival, enough energy and protein as well as micronutrients must still be provided in order to improve quality of life. Standard polymeric formulas can be suggested for these patients, without strict dietary advice.

Exercise prescription

Physical deconditioning is a frequent complication in patients with cirrhosis and end-stage liver disease, so in combination with nutritional treatment, a recommendation of physical exercise should be prescribed according to the characteristics of each patient.

Table 2 Branched-chain supplementation in patients with hepatocellular carcinoma

Ref.	Type of study	Population	Intervention (BCAA amount, time of supplementation)	Outcomes
Tada *et al*[63], 2019	Clinical trial (78 patients)	BCAA group: 27 patients Non-BCAA group: 51 Patients	5.712 g of L-leucine, 2.856 g of L-isoleucine, 3.432 g of L-valine. 18 mo	BCAA therapy was independently associated with good prognosis in patients with HCC (HR: 0.317, 95%CI = 0.123–0.813, P = 0.017). Multivariate analysis using competing risks methods indicated that BCAA therapy is independently associated with reduction of disease-specific mortality (HR: 0.216, 95%CI = 0.068–0.689, P = 0.001)
Nojiri *et al*[64], 2016	Randomized clinical trial (51 patients)	Control: 26 patients. Diet: Energy: 30–35 kcal/kg; Protein: 1–1.3 g/kg per day Intervention: 25 patients. Diet + Supplementation	420 kcal. 26.6 g of protein. 4.074 g of L-leucine. 3.845 g of L-isoleucine. 3.204 g of L-valine. 3 mo	Event-free survival was significantly higher in the BCAA group, whereas the intrahepatic recurrence rate was significantly lower (P = 0.04 and 0.036, respectively). A significant improvement in the SF-8 mental component score was observed in the BCAA group only (P < 0.01)
Ichikawa *et al*[65], 2013	Randomized clinical trial (56 patients)	Control: 30 patients. Standard diet Intervention: 26 patients. Standard diet + BCAA	1.144 g of L-isoleucine, 1.904 g of L-leucine, 0.952 g of L-valine. 2 wk before hepatic resection and 6 mo after.	There was no significant difference in the overall survival rate between the two patient groups. Recurrence rate at 30 mo after surgery was significantly better in the BCAA group in comparison to the control group. Tumor markers such as AFP and PIVKA-II, significantly decreased at 36 mo after liver resection in the BCAA group in comparison to the control group
Saito *et al*[66], 2014	Prospective cohort study (40 patients)	Control: 13 patients. Standard diet Intervention: 27 patients. Standard diet + BCAA	2.856 g of L-isoleucine, 5.712 g of L-leucine, 3.432 g of L-valine. > 3 mo	Supplementation with BCAA granules improves energy metabolism after RFA. BCAA granules improve the liver function after RFA. Improvements in the residual liver function may result in consistently adequate treatment for HCC recurrence after RFA
Nishikawa *et al*[52], 2012	Retrospective cohort study (99 patients)	Control = 59 patients. Regular diet Intervention: 40 patients. BCAA treatment	2.856 g L-isoleucine, 5.712 g L-leucine, 3.432 g L-valine. > 3 mo	Serum albumin level and Child-Pugh score improved significantly in the BCAA group as compared with the control 3 and 6 mo after TACE (P < 0.05)
Hayaishi *et al*[67], 2011	Randomized clinical trial (211 patients)	Control: 155 patients. Standard diet Intervention: 56 patients. Standard diet + BCAA	Intervention: 12 g/d BCAA (LIVACT Granules; Ajinomoto Co., Inc., Tokyo, Japan). > 6 mo	The incidence of HCC was significantly lower in the BCAA group than in the control group (HR: 0.416, 95%CI: 0.216–0.800, P = 0.0085). Oral BCAA supplementation also seems to be effective in the prevention of liver-related complications in patients with Child-Pugh A cirrhosis.
Hachiya *et al*[68], 2020	Randomized clinical trial (156 patients)	Control: 81 patients. Standard diet Intervention: 75 patients. Standard diet + BCAA	Intervention: 12 g/d BCAA (LIVACT Granules; Ajinomoto Co., Inc., Tokyo, Japan). 4 yr	BCAA supplementation may reduce tumor recurrence in low-risk patients. BCAA may not reduce the risk of tumor recurrence after hepatic resection in HCC in high-risk patients

AFP: Alpha-fetoprotein; BCAA: Branched-chain amino acid; CI: Confidence interval; HCC: Carcinoma hepatocellular; HR: Hazard ratio; PIVKA-II; Protein induced by vitamin K absence-II; RFA: Radiofrequency ablation; SF-8: School Form 8 Learner's Basic Health and Nutrition Report; TACE: Transcatheter arterial chemoembolization.

Although there are no specific recommendations for patients with cirrhosis and HCC, based on available evidence for cirrhosis some recommendations can be made. Generally, in extremely frail or malnourished patients, it is recommended to start with balance training to strengthen postural muscles and improve range of motion. Subsequently, to improve the condition of malnutrition and frailty, it is suggested to start with resistance exercises with light weight. In addition, at this point it is appropriate to start with aerobic exercise to improve cardiopulmonary endurance and overall fitness[35,53]. An easy and effective strategy to start physical training is to count the number of steps that a patient performs routinely during a week using pedometer-based bracelets to monitor exercise and to increase > 2500 per day above the number of basal steps, aiming to reach at least 5000 steps per day; this physical program has been carried out in patients with cirrhosis, finding beneficial results in body composition and nutritional status[54,55]. In addition to these effects, exercise improves quality of life and general wellness that are extremely important in patients

with cancer.

Finally, the professional healthcare involved in the nutritional management of patients with HCC and cirrhosis should always keep in mind the potential benefits of exercise and strongly encourage patients to perform an adequate exercise program, according to their functional status and comorbidities, especially for patients on the waiting list for liver transplantation[35,54].

CONCLUSION

HCC is a frequent type of cancer almost always coexisting with cirrhosis. Therefore, it is a challenging disease for healthcare providers. Malnutrition in these patients is associated with lower response to treatment and higher mortality, thus nutritional therapy including diet with sufficient energy and protein, supplementation with branched-chain amino acids as well as exercise must be implemented as part of the integral treatment.

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