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GUIDELINES AND CONSENSUS STATEMENTS

The second Mexican consensus on hepatocellular carcinoma. Part II: Treatment☆

L.E. Cisneros-Garza[a,*], M.S. González-Huezo[b], C. Moctezuma-Velázquez[c], L. Ladrón de Guevara-Cetina[d], M. Vilatobá[c], I. García-Juárez[c], R. Alvarado-Reyes[e], G.A. Álvarez-Treviño[f], S. Allende-Pérez[g], L. Bornstein-Quevedo[h], G. Calderillo-Ruiz[g], M.A. Carrillo-Martínez[i], M. Castillo-Barradas[j], E. Cerda-Reyes[k], J.A. Félix-Leyva[l], J.A. Gabutti-Thomas[c], J. Guerrero-Ixtlahuac[g], F. Higuera-de la Tijera[m], D. Huitzil-Melendez[c], E. Kimura-Hayama[n], P.A. López-Hernández[f], R. Malé-Velázquez[o], N. Méndez-Sánchez[p], M.A. Morales-Ruiz[q], E. Ruíz-García[g], J.F. Sánchez-Ávila[r], L. Torrecillas-Torres[d]

[a] *Hospital Christus Muguerza Alta Especialidad, Monterrey, Nuevo León, Mexico*
[b] *Centro Médico Issemym, Metepec, Estado de México, Mexico*
[c] *Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, CDMX, Mexico*
[d] *Centro Médico Nacional 20 de Noviembre, ISSSTE, CDMX, Mexico*
[e] *Hospital San Vicente, Monterrey, Nuevo León, Mexico*
[f] *Unidad de Medicina de Alta Especialidad 25, Monterrey, Nuevo León, Mexico*
[g] *Instituto Nacional de Cancerología, CDMX, Mexico*
[h] *InmunoQ, Laboratorio de Patología, Inmunohistoquímica y Biología Molecular, CDMX, Mexico*
[i] *Hospital San José Tec de Monterrey, Monterrey, Nuevo León, Mexico*
[j] *Centro Médico Nacional la Raza IMSS, CDMX, Mexico*
[k] *Hospital Central Militar, CDMX, Mexico*
[l] *Centro Médico Nacional Siglo XXI, IMSS, CDMX, Mexico*
[m] *Hospital General de México, CDMX, Mexico*
[n] *CTScanner Lomas Altas, CDMX, Mexico*
[o] *Instituto de Salud Digestiva y Hepática SA de CV, Guadalajara, Jalisco, Mexico*
[p] *Fundación Clínica Médica Sur, CDMX, Mexico*
[q] *Centro Oncológico Estatal Issemym, Toluca, Estado de México, Mexico*
[r] *Escuela de Medicina y Ciencias de la Salud, Tecnológico de Monterrey, Monterrey, Nuevo León, Mexico*

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Abstract Hepatocellular carcinoma (HCC) is more frequently manifesting as one of the main complications of cirrhosis of the liver, its principal risk factor. There have been modifications in its incidence over the past decade, related to an epidemiologic transition in the etiology

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* Corresponding author at: Edificio Médico de Especialistas, Hidalgo 2532 Col Obispado, Monterrey CP 64060, Nuevo León, Mexico. Tel.: +8181430424 and 8130689718.
E-mail address: laura_cisneros@yahoo.com (L.E. Cisneros-Garza).

Trasplantation;
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Systemic approach

of cirrhosis, with a decrease in the prevalence of hepatitis C and an increase in nonalcoholic fatty liver disease (NAFLD) as a cause, as well as the development of HCC in the non-cirrhotic liver due to NAFLD. Genetic markers associated with the disease have been identified, and surveillance and diagnosis have improved. Regarding treatment, surgical techniques, in both resection and transplantation, have advanced and radiologic techniques, at the curative stage of the disease, have enhanced survival in those patients. And finally, there have been radical changes in the systemic approach, with much more optimistic expectations, when compared with the options available a decade ago. Therefore, the *Asociación Mexicana de Hepatología* decided to carry out the Second Mexican Consensus on Hepatocellular Carcinoma, which is an updated review of the available national and international evidence on the epidemiology, risk factors, surveillance, diagnosis, and treatment of the disease, to offer the Mexican physician current information on the different topics regarding hepatocellular carcinoma. In this second part of the document, the topics related to the treatment of HCC are presented.

PALABRAS CLAVE
Ablación local;
Resección quirúrgica;
Trasplante;
Quimioembolización;
Terapia sistémica

II Consenso mexicano de carcinoma hepatocelular. Parte II: tratamiento

Resumen El Carcinoma Hepatocelular (CHC) se presenta cada vez más frecuentemente como una de las principales complicaciones de cirrosis, su principal factor de riesgo. La última década ha presentado modificaciones en su incidencia, relacionadas con una transición epidemiológica en la etiología de la cirrosis, con disminución en la prevalencia de hepatitis C y aumento en la etiología relacionada con la enfermedad por hígado graso no alcohólico (EHNA), además del desarrollo del CHC en hígado no cirrótico por EHNA. Se han identificado marcadores genéticos asociados a la enfermedad, así como avances en vigilancia y diagnóstico. En relación al tratamiento, el perfeccionamiento de técnicas quirúrgicas, tanto relacionadas con resección como trasplante; y radiológicas en estadios curativos permite mejorar la supervivencia de los pacientes candidatos a este abordaje; y finalmente, hay cambios radicales en el abordaje sistémico con expectativas mucho más optimistas cuando se comparan con lo disponible hace una década. Es por eso que la Asociación Mexicana de Hepatología decidió realizar el II Consenso Mexicano de Carcinoma Hepatocelular, en el cual se hizo una revisión actualizada de la evidencia disponible nacional e internacional sobre la epidemiología, factores de riesgo, vigilancia, diagnóstico y tratamiento de la enfermedad; con el objetivo de ofrecer al médico mexicano una revisión actualizada sobre los diferentes tópicos de esta enfermedad. En esta segunda parte del documento se presenta los tópicos relacionados con el tratamiento del CHC.

Curative approaches

Coordinator: Dr. Mario Vilatobá.

Participants: Ricardo Alvarado Reyes, Miguel Ángel Carrillo Martínez, Laura Torrecillas Torres, Eira Cerda Reyes, JA Gabutti Thomas.

25. All hepatocellular carcinoma (HCC) patients treated with curative intent through thermal ablation therapies (radiofrequency ablation [RFA], microwave ablation [MWA], cryoablation [CA]), intra-arterial radiotherapy with yttrium-90 (Y-90), or hepatectomy should first undergo non-contrast-enhanced chest computed tomography imaging and bone scintigraphy.

In complete agreement: 100%.

Any patient diagnosed with HCC that is considered for curative-intent treatment, should first be staged through imaging studies[1]. The most frequent extrahepatic metastases sites are the lung, bone, and lymph nodes, but metastases can also present in the adrenal glands and peritoneal cavity[2]. Therefore, given the most frequent metastasis sites, in addition to triple-phase computed tomography (CT) scanning of the liver and abdomen or dynamic magnetic resonance imaging (MRI), non-contrast-enhanced chest CT and bone scintigraphy are recommended. Even though F-18 fluorodeoxyglucose positron emission tomography (FDG-PET) is very helpful for staging and diagnosing different types of malignant tumors, its usefulness for detecting extrahepatic metastases in HCC is

limited because of its low sensitivity (64%) and high cost[3,4].

26. Thermal ablation therapies are indicated in the curative-intent treatment of HCC in cirrhotic patients with Child-Pugh class A disease, a MELD score ≤9, and a lesion ≤3 cm, especially in nonperipheral lesions.

In complete agreement: 98.31%; in partial agreement: 1.69%.

Over the past 2 decades, there has been great interest worldwide in locoregional ablation therapies, including RFA, MWA, CA, ethanol injection, acetic acid injection, high-intensity focused ultrasound, and laser-induced thermal therapy. Among those, RFA has been the most widely studied and for several years has emerged as a very useful therapy for HCC tumors ≤3 cm, in patients with good liver function (Child-Pugh class A, MELD score ≤9)[5].

More recently, other ablation therapies, such as MWA and CA have shown good results, thanks to technologic advances. Several studies show them to be as effective as surgical resection and RFA in HCC ≤3 cm, with an overall survival rate of 60–80%[6–9].

In a multicenter meta-analysis, RFA and liver resection were compared in patients with HCC and Child-Pugh class A cirrhosis. Overall survival and disease-free survival were evaluated, and no differences were found in 1 and 3-year overall survival and 3-year disease-free survival[10].

In another meta-analysis, Zhang et al. included 5 nonrandomized controlled studies. Of the 543 patients, 243 were treated with RFA and 300 with liver resection, finding no differences in the survival and recurrence rates in tumors ≤3 cm. The group treated with RFA had fewer complications[11].

In a systematic review and meta-analysis that included 43 studies, Tiong and Maddern analyzed randomized controlled trials and nonrandomized comparative studies, with follow-up periods for more than 12 months. They found no significant difference in the survival rate, between RFA and liver resection. However, there was less recurrence in the liver resection group[5].

In a prospective and randomized study, Chen et al. reported that RFA was efficient and comparable to hepatectomy in overall survival and disease-free survival in tumors ≤3 cm. Recurrence was higher in the RFA group, but there was no significant difference in survival[12].

Lastly, Pompili et al. analyzed 544 patients at 15 Italian centers, with Child-Pugh class A cirrhosis and HCC ≤3 cm (246 patients in the liver resection group and 298 in the RFA group). Despite the higher local recurrence, the RFA group had results comparable to those of the liver resection group[13].

27. When thermal ablation cannot be performed, due to lack of resources or because it is not technically possible, chemical ablation therapies, such as ethanol ablation, should be considered in the curative-intent treatment of HCC, in cirrhotic patients with Child-Pugh class A disease, a MELD score ≤9, and a lesion ≤2 cm.

In complete agreement: 96.15%; uncertain: 3.85%.

Percutaneous absolute ethanol injection is an ablation technique that has excellent results in tumors ≤2 cm, reaching complete tumor necrosis in the majority of cases[14,15]. Tumors >2 cm tend to have intralesional fibrotic septa that limit the diffusion of the ethanol, reducing its efficacy[16].

That technique can be considered an alternative to thermal ablation therapies at centers with limited resources[14,15]. Chemical ablation can be employed in tumors that are close to vascular, biliary, or intestinal structures, in which thermal ablation can cause considerable collateral damage[14].

Randomized clinical trials have shown that RFA is superior to chemical ablation with ethanol: the complete response rate was 96% vs. 88% and 3-year disease-free survival was 34–49 % vs. 12–43%[17], but those studies included HCC > 2 cm.

Regarding local recurrence, RFA is superior to ethanol injection (hazard ratio [HR] 0.38, 95% CI 0.15—0.96; $p = 0.040$), but there was no difference between the ablation techniques, with respect to distant intrahepatic recurrence (HR 0.95, 95% CI 0.75–1.22, $p = 0.707$, $I^2 = 0.0\%$)[18].

Ethanol ablation has a high safety profile. In a systematic review of 4 randomized clinical trials, there was a higher percentage of serious complications in the RFA group vs. the ethanol group, 3.7% vs. 1.5% (HR 2.04, 95% CI 0.81–5.15, $p = 0.059$)[18].

The advantage in overall survival of RFA over ethanol ablation is less clear. In a meta-analysis that included 8 randomized clinical studies, overall survival was superior in the patients that underwent RFA as treatment for HCC (HR 0.67, 95% CI 0.51—0.87; $p < 0.001$)[19]. However, that difference was not significant when the Asian studies were excluded; there was only a trend favoring better survival in the RFA group. Those results reflect the geographic heterogeneity of the disease.

A technical aspect to consider is the number of sessions required to reach complete tumor necrosis (1.1 sessions of RFA vs. 5.4 sessions of ethanol injection)[20]. Given that a high number of sessions can compromise the benefit-cost ratio of ethanol ablation, patients must be adequately selected.

In conclusion, in centers with limited resources, curative-intent chemical ablation with ethanol can be carried out in HCC tumors <2 cm, especially when thermal ablation is not technically possible. It has a high safety profile. With respect to overall survival and recurrence, the presently available information is heterogeneous and further study is required, especially regarding small tumors.

28. In patients with Child-Pugh class A disease or a MELD score <9, thermal ablation has the same overall survival results as hepatectomy, in HCC tumors <3 cm.

In complete agreement: 96.5%; in partial agreement: 3.85%.

Surgical resection of HCC is the ideal treatment in patients with early-stage disease and conserved liver function, but up to 70% of patients develop recurrent disease[21].

Thermal ablation is efficacious in tumors <3 cm that have a round/elliptical morphology[16]. The majority of commercial needles provide an ablation area in that shape, with a diameter of 4—5 cm. A safe peritumoral ablation edge of at least 0.5 cm must always be considered.

Three randomized clinical trials[17–19] open the debate on the superiority of surgery vs. thermal ablation, especially RFA at early stages (single tumor <3 cm) and very early stages (single tumor <2 cm)[22].

The results of the 3 main randomized clinical trials plus the information from 25 nonrandomized studies were evaluated through a meta-analysis published in 2014[23]. In that study, there was no significant difference in overall survival

at 1, 3, and 4 years in patients with HCC <3 cm after surgical resection or RFA.

Nevertheless, nonrandomized studies tend to favor surgery, in terms of overall survival, which can be explained by selection bias. Patients in better general conditions are the preferred candidates for surgical treatment, whereas patients with limited liver reserve or important comorbidities tend to receive ablation as first-line treatment[22].

As to safety and cost-effectiveness, RFA has been shown to be superior to surgery, in the context of early disease[23,24].

There was no difference regarding in-hospital mortality between the two groups[23].

The complication rate was lower in patients that underwent RFA vs. surgical resection (5.9 vs. 34.6, relative risk [RR] 0.18, 95% CI 0.06—0.53, number-needed-to-treat = 4)[23]. Likewise, hospital stay in patients that underwent RFA was a mean 6.7 days fewer than that for surgical resection.

In conclusion, with respect to thermal ablation, the most widely studied technique is RFA, which has been shown to be as effective as surgery in the treatment of early and very early HCC. Maintaining said equality, safety, and cost-effectiveness depends on the adequate selection of the cases to be treated with RFA, based on tumor location, morphology, and size[24].

29. Hepatectomy in HCC is indicated in patients with a healthy liver, as long as the residual liver volume (RLV) is ≥30%, *taking a surgical mortality rate <5% into account.*

In complete agreement: 100%.

The incidence of HCC in the non-cirrhotic liver is estimated at around 15–20% of all HCC. The ''normal'' quality of the non-tumor liver parenchyma makes HCC in the non-cirrhotic liver a very different entity, with respect to its epidemiology, clinical presentation, management, and prognosis[25]. The mean age in non-cirrhotic patients is generally lower than in cirrhotic patients[26]. HCC in the non-cirrhotic liver tends to be larger at diagnosis, given that the patients are not enrolled in surveillance programs. The specificity of the distinctive images in cirrhotic livers (hyperuptake in the arterial phase and washout in the portal venous and late phases) does not apply in the context of a healthy liver. Thus, the diagnosis of HCC in a patient with no cirrhosis requires biopsy and histologic study of the tumor.

Liver resection is the treatment of choice for HCC in non-cirrhotic patients (5% of the cases in the West, 40% in Asia)[27,28], as long as extrahepatic disease is ruled out through chest and abdomen CT and bone scintigraphy, and a RLV >30% is considered[29,30]. It should be kept in mind that it is not very common for HCC to present in a liver with no underlying pathology, thus the importance of evaluating the presence of fibrosis, steatosis, or steatohepatitis, in patients in whom resection is planned, and in cases of doubt, a biopsy of non-neoplastic liver tissue should be performed before the procedure[31]. If there is an alteration in the liver parenchyma, resecting a larger remnant of the liver must be considered, depending on the hepatic involvement. If the patient does not have an adequate RLV (>30% of the standard liver volume [SLV]), portal embolization (PE) should be contemplated to create hypertrophy in the healthy lobe[32].

30. Hepatectomy is indicated in HCC in the cirrhotic liver, as long as the patient has Child-Pugh class A disease, a MELD score ≤*9, RLV* ≥50%, *and does not present with clinically significant portal hypertension, taking a surgical mortality rate <5% into account.*

In complete agreement: 96.15%; in partial agreement: 3.85%.

Surgical resection is the treatment of choice in Child-Pugh class A cirrhotic patients, with sufficient functional liver reserve. The commonly accepted and utilized criteria for liver resection are functional Child-Pugh class A, Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, indocyanine green retention rate, portal hypertension, serum bilirubin, and RLV[33].

The indocyanine green retention rate at 15 min (ICG-R15) is widely used in Asia, and increasingly utilized in European institutions. A larger liver resection (≥3 segments) can be performed when the ICG-R15 is ≤10%, as well as in the absence of significant portal hypertension and in patients with a MELD score ≤9[34]. That method is currently unavailable in Mexico.

With respect to RLV, it should be ≥50%, calculating the SLV and RLV, the latter through liver volumetry in tomography. If the RLV is <50%, there are strategies for stimulating hypertrophy of the liver, such as PE, portal vein ligation, suprahepatic embolization, and associating liver partition and portal vein ligation for staged hepatectomy (ALPPS). PE is currently considered the first choice because of its lower morbidity and mortality rates. However, ALPPS is recognized as a strategy that achieves considerable hypertrophy in a shorter period of time, but with greater morbidity and mortality. Multicenter studies have shown mortality rates of 1–5% and morbidity rates of 30–40% after liver resection. Overall survival and disease-free survival rates are 46–69.5% and 23–56.3%, respectively. The 5-year recurrence rate is from 43.7–77%, and is generally intrahepatic[32,35].

31. Smaller hepatectomies (1 or 2 segments) can sometimes be contemplated in patients with HCC and portal hypertension, as long as total bilirubin levels are ≤*2 mg/dl and there are no clinical signs of ascites.*

In complete agreement: 92%; in partial agreement: 8%.

Even though hepatectomy is currently considered in cirrhotic patients with Child-Pugh class A and no clinical signs of portal hypertension, there are increasingly more publications questioning those criteria and proposing the broadening of surgical indication in certain cases, without compromising the results[36]. Ascites and a bilirubin level ≥2 mg/dl are considered independent variables for a higher risk of decompensation and postoperative liver failure[37], and so cases must be very well selected. According to the Liver Cancer Study Group of Japan and the Makuuchi criteria, even in the presence of portal hypertension, if the patient does not present with signs of ascites and indocyanine green clearance is adequate, a right or left hepatectomy can be performed, as long as the total bilirubin level is normal. If total bilirubin levels are between 1.1 and 1.5 mg/dl, left lateral hepatectomy or right posterior hepatectomy can be carried out. When the serum bilirubin level is between 1.6 and 1.9 mg/dl, only limited resections can be performed[38].

32. Laparoscopic hepatectomy (LH) is well accepted in single tumors located on the periphery, especially in the left lateral lobe, with similar overall survival and recurrence-free survival, when compared with open hepatectomy.

In complete agreement: 96.15%; in partial agreement: 3.85%.

There are very few randomized trials that compare LH vs. open hepatectomy (OH), but LH has been gaining ground in HCC. El-Gendi et al. conducted a randomized controlled study comparing OH vs. LH. With 25 patients per group, they found that surgical time and hospital stay were significantly better in LH and that there were no differences with respect to surgical complications and need for transfusion. After follow-up with a mean of 34.43 months (31.67–38.60), LH had an adequate oncologic result, compared with OH. Disease-free survival at 1 year and 3 years was 88 and 59% in the LH group and 84 and 54% in the OH group ($p = 0.9$)[39].

In the second International Consensus on Laparoscopic Hepatectomy, the participating experts validated LH for minor resections. Currently, resections for HCC located in the peripheral segments, especially in the left lateral lobe, are performed laparoscopically in the majority of hepatobiliary surgery centers[40].

For now, the limits of LH are still to be defined, especially regarding major and complex hepatectomies.

The benefits of laparoscopy are the hemostatic effect of the pneumoperitoneum, increased visibility due to magnification, less manipulation, and less respiratory involvement. All those are contributing factors to the better results seen in patients with HCC and cirrhosis, with a lower frequency of decompensation and ascites[41].

In a recent meta-analysis, 51 retrospective studies were analyzed that compared LH vs. OH and included 6812 patients[42]. LH was associated with less blood loss, lower morbidity and mortality at 30 days, and shorter hospital stay. R0 resection (resection with negative microscopic margins) was comparable between the groups and there was also a trend towards less recurrence and longer survival with LH.

Prospective, randomized studies on LH for treating colorectal metastases showed lower morbidity in minor hepatectomies[43]. Similar studies on HCC are currently in process.

33. The main limitation of the thermal ablation therapies and liver resection in patients with cirrhosis and HCC is recurrence, with a 10-year recurrence-free survival rate of 20–25%.

In complete agreement: 92.31%; in partial agreement: 7.69%.

Patients with preserved liver function (Child-Pugh Class A, MELD score $\leq$9, and no clinical signs of portal hypertension) can undergo hepatectomy or a thermal ablation therapy (RFA) in tumors $\leq$3 cm. Nevertheless, tumor recurrence, after those treatments, is 50–70 % at 5 years. Despite the possibility, it is difficult to consider a patient with cirrhosis and resected HCC as cured. Utilizing the database of the National Registry of Japan, 20,811 patients with HCC that underwent curative-intent surgery were analyzed, resulting in a 10-year recurrence-free survival of 22.4%. A small number of patients ($n = 281$) were recurrence-free after 10 years. Of that group, 83% had a tumor <5 cm, 91% were single tumors, 61.3% were moderately differentiated tumors, and 98.6% had no vascular invasion or intrahepatic metastasis. When the 10-year recurrence-free group was compared with a group that died within the first 5 years ($n = 918$), the multivariate analysis showed that tumor differentiation was the most important predictor of death due to HCC recurrence within the first 5 years, given that patients with poorly differentiated tumors had a 3.33-times higher risk of death[44].

An Italian retrospective multicenter study evaluated the long-term results of patients with HCC $\leq$3 cm treated with liver resection. In 588 patients from 8 centers, 23% had microsatellite nodules and 37% had microvascular invasion. Overall survival was 52.8 and 20.3% and disease-free survival was 32.4 and 21.7%, at 5 and 10 years, respectively. Microsatellite lesion was the only independent factor associated with poor overall survival and disease-free survival[45].

Surgical resection extension (anatomic resection [AR] vs. non-anatomic resection) continues to be a subject of debate. Theoretically, AR is considered more efficacious in oncologic terms and with respect to the eradication of micrometastases[46,47].

34. If there is recurrence after hepatectomy or thermal ablation therapy with curative intent, the patient can be considered for salvage liver transplantation (SLT), as long as he/she meets the Milan or University of California at San Francisco (UCSF) criteria and has an alpha-fetoprotein (AFP) level <1000 *ng/mL. Survival is similar to that of patients with initial liver transplantation.*

In complete agreement: 92.31%; in partial agreement: 7.69%.

Patients that present with recurrence after curative-intent treatment can be considered for SLT. That modality can be used in 50–60% of cases, with an intention-to-treat survival rate >80% at 10 years in patients that had no recurrence or were treated with SLT[48]. Importantly, resected early-stage HCC is a predictor for greater SLT success[49]. Patients with a single tumor <3 cm have a 10–30% possibility for recurrence outside of the Milan criteria, and therefore, the majority will be candidates for SLT[50]. A meta-analysis reported a better post-SLT survival at 5 years with initial liver transplantation (LT) and concluded that SLT could be a better strategy for HCC that recurs, in patients with adequate liver function that are eligible for initial resection[51]. LT after the resection of a high-risk tumor (microvascular invasion and/or satellite lesions)[52], without waiting for recurrence, must be validated through further studies.

35. LT should be performed on patients with HCC that meet the Milan or UCSF criteria and have AFP levels <1000 *ng/mL, after locoregional treatment and a waiting period of 3–6 months.*

In complete agreement: 96.15%; in partial agreement: 3.85%.

The Milan criteria (a lesion $\leq$5 cm or 3 lesions, none of which is >3 cm), published by Mazzaferro et al. in 1996[53], have been the most widely recommended criteria internationally. When met, the results at 4 years are excellent, with an 85% survival rate and a recurrence rate of only 8%. However, the desire to extend them has resulted in a series of proposals from different centers worldwide[54].

The UCSF criteria have been the most validated extended criteria, with respect to both imaging and pathology[55]. With those criteria (a lesion $\leq$6.5 cm or 3 lesions, each $\leq$4.5 cm, and a total tumor volume $\leq$8 cm), 5-year recurrence-free survival was 80%, and they are currently used by a large number of centers worldwide.

The fact that post-transplantation progression in HCC largely depends on tumor biology is being increasingly recognized, making an approach involving only the number and size of tumors incomplete. Therefore, biologic markers,

such as AFP, AFP-L3, and des-gamma-carboxy prothrombin have recently become more relevant[56–58].

Of those biomarkers, AFP is currently the most widely utilized for determining the prognosis of post-LT HCC. An AFP level >1000 ng/mL, nonresponsive to locoregional treatment, is associated with lower survival in patients with HCC. Ideally, AFP should be <500 ng/mL after treatment[59,60].

Another aspect dependent on tumor biology is the response to locoregional therapies (transarterial chemoembolization [TACE], Y-90, or RFA). Patients with disease progression, despite locoregional therapy, have a worse prognosis than those that respond to treatment[61,62]. There is increasing evidence that progression is good in cases of LT due to HCC, when the response to locoregional therapies has been good, the tumors are within the Milan criteria or the UCSF criteria, and when there is a period of waiting of at least 3 months after locoregional therapy[63].

Currently, all patients within the Milan or UCSF criteria that have an AFP level <1000 ng/mL, can undergo transplantation after locoregional therapy and a waiting period of 3–6 months.

36. Patients that meet the Milan and UCSF criteria, with AFP levels <1000 ng/mL, and after bridging therapy, with a waiting time of 3–6 months, should be prioritized on the waiting list if they have a MELD score of 22.

In complete agreement: 84.62%; in partial agreement: 11.54%; uncertain: 3.85%.

Patients with HCC that are registered for LT normally receive exception points, given that they have compensated liver function and a low MELD score. The adjustment should also be made, depending on the projection of tumor progression risk on the waiting list.

In the United States, exception points for HCC initially gave HCC patients a greater transplantation advantage over those that did not have HCC[64]. That system is no longer valid, and over time, the exception policy has been modified on various occasions to make it as fair as possible, among the different United Network of Organ Sharing regions. A mandatory waiting period of 6 months has recently been included for all patients with HCC, before receiving exception points, after which they are assigned a MELD score of 28 that is increased every 3 months until reaching the limit of 34[65].

A way to calculate MELD exceptions in HCC, to list a patient for LT, is through the MmaT-3. It consists of taking into consideration all the LTs performed within 250 nautical miles of the program in the past 365 days. A median MELD score is thus calculated and assigned to the patient with HCC.

In Mexico, there is not enough information for issuing a clear policy, given the scarcity of results on the topic. Nevertheless, there are reports that transplantations are performed with a mean MELD exception point between 19 and 22 at some Mexican centers[66]. It appears that a MELD exception point of 22 in patients with HCC, after a post-locoregional treatment waiting period of at least 3 months, is adequate and fair.

Increasing the points every 3 months also appears to be controversial and there is no evidence enabling any decision-making on the subject. Without a doubt, national policies in this regard are a pending concern for patients with HCC, given that at present each liver transplantation center decides which criteria should be considered and whether or not HCC patients are prioritized.

37. Patients that do not meet the Milan or UCSF criteria can be considered for LT, as long as they meet the UCSF down-staging (DS) protocol and have an AFP level <1000 ng/mL.

In complete agreement: 96%; in partial agreement: 4%.

DS consists of utilizing locoregional therapies (TACE, and more recently, radioembolization with Y-90)[67] to reduce tumor size until it is viable, within certain criteria. The majority of studies consider that the tumors should be within the Milan criteria[68]. The purpose of DS is to serve as a selection tool for patients with HCC outside of the Milan and UCSF criteria, that if responsive to treatment, could undergo transplantation with good results. Initially, the patients that were able to meet the Milan criteria through DS had the same progression as patients that had always met the Milan criteria[69,70]. The United States adopted the DS criteria of the UCSF[69]. The protocol consists of a single lesion $\leq$8 cm, or 2–3 lesions <5 cm with a total tumor diameter $\leq$8 cm, or 4–5 lesions, all $\leq$3 cm, with a total diameter $\leq$8 cm and a minimum observation period of 3 months. Because of the risk for liver function decompensation, that treatment is recommended in patients with Child-Pugh class A or B and total bilirubin levels $\leq$3 mg/dl[67].

The inclusion of patients for DS that have tumors outside of the Milan criteria, known as ''all comers'', has shown less favorable results than those of patients that have always met the Milan criteria or that met the DS protocol. Mehta et al. reported a 3-year survival rate of 83% in patients that met the Milan criteria, compared with 79% in patients that were down-staged with the above-mentioned protocol. In contrast, the 3-year survival in the ''all comers'' was considerably lower, at 71%[71]. Therefore, more evidence is needed to justify the acceptance for LT in patients with HCC outside of the UCSF criteria for DS.

38. There are currently no benefits in receiving adjuvant therapy after RFA, hepatectomy and/or LT.

In complete agreement: 96.15%; in partial agreement: 3.85%.

Even though recurrence after liver resections for HCC can be as high as 70% at 5 years[72], there is still no generally accepted adjuvant therapy, and so neither the American nor the European guidelines on the study of the liver provides any recommendations[33,73]. Studies have been conducted on different treatments, including sorafenib (SOR)[74], without being able to demonstrate a benefit in recurrence-free survival. The advent of new treatments with anti-PD-1 monoclonal antibodies could change that situation[75].

With respect to LT, except for the abovementioned ablation therapies, there is no study that shows the benefit of giving systemic adjuvant therapy. A prospective, randomized, double-blinded phase III study was conducted on neoadjuvant therapy with SOR + TACE or TACE + placebo and showed no benefits[76].

39. There is presently insufficient evidence for deciding upon using specific immunosuppression in patients after LT due to HCC.

In complete agreement: 96.15%; in partial agreement: 3.85%.

Experimental studies have shown that calcineurin inhibitors promote tumor formation[77]. In addition, observational and retrospective studies have reported that both tacrolimus and cyclosporine, especially at high doses, increase HCC recurrence[78,79].

The mTOR inhibitors – sirolimus and everolimus – in addition to their immunosuppressive effects, target some pathways utilized by HCC, and have shown antiproliferative and antiangiogenic properties[80]. In retrospective studies and some meta-analyses, patients that received immunosuppression with mTOR inhibitors had less risk for developing HCC recurrence[81,82]. However, there is no evidence demonstrating that HCC is really sensitive to mTOR inhibitors in non-transplanted patients, even at higher doses than those used post-transplantation[83]. There is only one prospective, multicenter, randomized study on transplant patients that compares immunosuppression with sirolimus vs. sirolimus-free immunosuppression in LT due to HCC. After 5 years of follow-up, there was no difference in overall survival or in recurrence-free survival, and paradoxically, low-risk patients (those always within the Milan criteria) presented with a certain benefit upon receiving sirolimus. A recent consensus by the International Liver Transplantation Society (ILTS) states that even though retrospective studies favor mTOR inhibitor use, there is no evidence for recommending a specific type of immunosuppression in patients undergoing LT due to HCC. Calcineurin inhibitor use is recommended, with trough levels of tacrolimus <10 ng/mL and cyclosporine <300 ng/mL[84].

Non-curative approaches

Coordinator: Ignacio García-Juárez.

Participants: Jorge Guerrero Ixtlahuac, Erika Ruíz-García, David Huitzil Melendez, Mauricio Castillo Barradas, Silvia Allende Pérez, Jesús A Félix Leyva, Guillermo Alberto Álvarez Treviño.

40. The non-curative locoregional therapy for HCC with the greatest impact is transarterial embolization (TAE).

In complete agreement: 100%.

Non-curative interventional therapies for HCC management are transarterial embolization, with or without intra-arterial chemotherapy (TACE and TAE, respectively), transarterial radioembolization with Y-90, stereotactic body radiotherapy (SBRT), and SBRT in combination with systemic chemotherapy[85].

The use of locoregional therapies (alone or in combination) for HCC is recommended over conservative treatment in patients with tumors larger than 3 cm, multinodular disease (>4 nodules), no vascular invasion or extrahepatic disease, with an ECOG performance status of 0, and stable Child-Pugh class A liver function[86,87].

A network meta-analysis that included 55 randomized controlled trials, with a total of 5763 patients with stable liver function and unresectable HCC, showed that embolization methods achieved better survival, compared with control treatment (HR 0.42)[88].

The most widely used therapies in Mexico are TAE and TACE, albeit neither is preferred over the other; the choice is based on the experience of the interventional radiologist. According to different studies, there is no superiority of TACE vs. TAE, and a systematic review with 6 controlled clinical trials and a total of 676 patients showed no difference in 3-year survival (RR: 0.97, 0.74–1.27; $p = 0.81$) between the two strategies, nor did it show a difference in disease-free progression ($p = 0.40$), but it did show a greater toxicity in the treatment with TACE (RR: 1.44, 1.08–1.92; $p = 0.01$). However, one of the limitations of those studies was the fact that their results could have been affected by the heterogeneity in the different TACE techniques[89].

41. Other developing locoregional therapies are transarterial radioembolization with Y-90 and SBRT, among others.

In complete agreement: 96%; in partial agreement: 4%.

With respect to overall survival, there are no significant differences regarding the type of locoregional therapy administered, when drug eluding bead (DEB)-TACE, Y-90, and TAE are compared (OR 0.85–1.65). Likewise, the choice is determined by the experience of the interventional radiologist and/or the protocol of each hospital center. A mean overall survival of 20.8 months is estimated in patients treated with TAE, 18.1 months in patients with TACE, and 20.6 months in patients undergoing DEB-TACE[88].

Compared with conventional TACE, DEB-TACE achieves a high concentration of the drug, limited to the intratumoral space, conditioning a better local response, lower recurrence rate, and ultimately, less systemic and hepatic toxicity[90,91].

Transarterial radioembolization with Y-90 is not recommended as first-line therapy for the treatment of HCC at intermediate or advanced stages. Despite the fact that phase II and III studies have shown delay in tumor progression with a fewer number of adverse effects, an increase in overall survival, compared with systemic therapy with SOR, has not been demonstrated[90]. Y-90 is indicated in patients with portal venous thrombosis because of its mechanism of action that conditions minimal ischemic effects. Y-90 is utilized for treating HCC in patients at intermediate or advanced disease stages that have poor tolerance to management with TACE or SOR. Its mechanism of action is based on an intra-arterial treatment of β radiation-emitting Y-90 microspheres, but unlike TACE, it has no ischemic effect. Radiation penetration is 2.5 mm, preventing damage to the adjacent liver parenchyma[92]. One of the advantages of radioembolization with Y-90, compared with TACE and DEB-TACE, is that it produces more extensive tumor necrosis, without conditioning ischemia, reducing the risk of local progression. It is superior for achieving tumor reduction and induces compensatory liver hypertrophy[93]. For optimum results, follow-up and the evaluation of a repeat session is recommended, given that a greater impact on partial and complete response rates can be achieved, compared with patients that undergo only one session.

Regarding results, the embolizing therapies (TAE, TACE, DEB-TACE) provide a partial response in approximately 53% of patients after a single session, and up to 87.3%, with repeat sessions[94]. Retreatment with 2 and 3 TACE sessions in lesions smaller than 5 cm shows a complete response of 55 and 40%, respectively, and retreatment with 2 and 3 sessions in lesions larger than 5 cm achieves complete response of 25 and 2%, respectively[91].

The use of combined locoregional therapies is recommended for treating lesions larger than 3 cm. The combination of RFA and TACE is justified due to the limited

tumor control of ablation in lesions larger than 3 cm. A meta-analysis of 8 randomized controlled clinical trials in patients with lesions larger than 3 cm showed higher survival in the combined therapy group, compared with the group that only received TACE, and the complication rate was not higher[95].

The use of the combination therapy of TACE + RFA has results similar to those of surgery, in terms of survival and the disease-free period. A meta-analysis compared the use of that combination of locoregional therapy vs. surgical treatment and found no significant difference in overall survival at 3 and 5 years (OR 0.91; $p = 0.68$) or in the recurrence-free period (OR 1.00; $p = 1.00$), with a higher complication rate in the surgical group vs. the TACE + RFA combination group[96]. In contrast, when TACE alone vs. surgical treatment is compared in patients with single tumors larger than 5 cm, greater 3 and 5-year survival is shown in patients undergoing surgery (HR 0.6; $p < 0.001$), as well as a longer time to progression[97].

The combination of DEB-TACE + RFA has results similar to those reported with the combination of TACE + RFA. There is improvement in survival and the disease-free period with the two combination therapies vs. DEB-TACE alone. In a single center prospective study, 40 patients with HCC larger than 3 cm underwent the combination therapy of DEB-TACE + RFA and 20 patients had monotherapy with DEB-TACE. There was complete response in 80% of the patients with the combination therapy (32/40) and complete response in 40% of the patients that underwent monotherapy (8/20); the rest of the patients in both groups had partial response. The group treated with the combination locoregional therapy had a lower recurrence rate at 2 years (48.1% vs. 78.2%; $p > 0.001$) and greater survival (91.1% vs. 60.6%; $p = 0.004$), compared with the group treated with monotherapy[98].

The combination of systemic therapy utilizing the multikinase inhibitor, SOR, and the locoregional therapy, TACE, is based on achieving the association of embolization-induced hypoxemia with the antiangiogenic mechanism of the drug, to prolong time to tumor progression, and consequently, prolong survival. A meta-analysis with 6 studies reported a greater survival rate with the combination therapy, compared with TACE as monotherapy, but larger randomized clinical trials that compared the combination of DEB-TACE plus multikinase inhibitors vs. DEB-TACE alone, showed no greater clinical benefit[99,100].

The use of combined locoregional therapies (embolization and ablation) plus immunotherapy, is currently being developed and has shown good preliminary results in relation to long-term response, in addition to documenting response, in some cases, regarding distant metastasis, called the abscopal effect.

Non-curative locoregional therapies condition changes in the HCC microenvironment, producing an immune response, which can be strengthened with treatment based on immunotherapy (immune checkpoint inhibitors)[101]. The synergic effect of the combination of those therapies (locoregional treatment plus immunotherapy) promotes the effects of the exposure to tumor antigens for a longer period of time, achieving greater long-term antitumor immune response[102]. Numerous phase II studies are currently being conducted to prove that hypothesis, combining immune checkpoint inhibitors with locoregional therapies (Table 1)[101].

The support of the interventional radiologist in the placement of intra-arterial ports has satisfactorily contributed to hepatic arterial infusion chemotherapy (HAIC), which increases progression-free survival and overall survival. HAIC is a minimally invasive technique that consists of chemotherapy infusion through a reservoir that is subcutaneously implanted 2 cm from the anterior superior iliac spine and an intra-arterial catheter placed in the hepatic artery through the femoral approach[102]. The technique has been shown to increase progression-free survival and overall survival, with a decrease in adverse effects, compared with TACE[103].

42. The choice of first-line systemic therapy (category 1) is individualized, based on tumor characteristics, liver reserve, the performance status of the individual, and the efficacy and safety of the available drug.

In complete agreement: 96%; in partial agreement: 4%.

The treatment goal is to increase overall survival with the best quality of life possible, which is done by choosing the optimum strategy according to the tumor stage of each patient. Likewise, adequate candidate selection is required[85]. The indication for treatment should be evaluated on a case-by-case basis, and if the patient is not a candidate for first-line treatment due to his or her disease stage, the next best option for that stage of disease, or the treatment for a more advanced stage, should be considered.

In the treatment of advanced disease, the presence of portal invasion, extrahepatic extension, and liver function, utilizing the Child-Pugh score, should be evaluated, with preference for an ECOG performance status of 1–2[104,105]. The presence of liver decompensation, manifested as jaundice, variceal bleeding, encephalopathy, or ascites, should be considered a contraindication for any locoregional therapy that can produce greater liver injury. At present, the benefit of systemic therapies in patients with liver decompensation has not been clearly defined[105].

43. The accepted first-line systemic therapies (category 1) in advanced HCC are sorafenib, lenvatinib (LEN), and atezolizumab + bevacizumab.

In complete agreement: 100%.

SOR was the first available oral multikinase inhibitor. It acts on multiple targets, including the vascular endothelial growth factor receptor (VEGFR)-1, VEGFR-2, and VEGFR-3, the beta type platelet-derived growth factor receptor (PDGFR), and the RAF and BRAF pathways[106]. It was approved for treatment of advanced HCC in 2007. The drug's mechanism of action provides it with an antiangiogenic and antiproliferative effect. Its efficacy was documented in the phase III SHARP pivot study[107] that included 602 patients with unresectable advanced HCC, with no previous treatment, an ECOG performance status of 0–2, Child-Pugh class A liver function (ultimately, 5% of patients with Child-Pugh class B were included), adequate kidney function, adequate hematologic function, and a life expectancy greater than 12 weeks. The patients were randomized to receive oral SOR 400 mg twice a day, continuously, vs. placebo, until disease progression or toxicity. The primary aims were overall survival and time to symptomatic progression and the secondary aim was time to radiologic progression. Mean survival was 10.7 months for SOR vs. 7.9 months for the placebo group (HR 0.69, IC 95% 0.55—0.87; $p < 0.001$). There was no statistically significant difference between the two groups, regarding the mean time to symptomatic progression (4.1

Table 1 Clinical trials registered by August 22, 2019.

ClinicalTrials.gov identification number	Locoregional therapy	Drug under study	Line of therapy
NCT03817736	TAE and SBRT	Immune checkpoint inhibitor	Sequential
NCT03638141	DEB-TACE	Durvalumab and tremelimumab	Sequential
NCT03143270	TAE	Nivolumab	Combination
NCT03572582	TAE	Nivolumab	Combination
NCT03397654	TAE	Pembrolizumab	Sequential
NCT03383458	Ablation	Nivolumab	Adjuvant
NCT02821754	TAE, RFA, CA	Durvalumab, tremelimumab	Combination
NCT02837029	Y-90	Nivolumab	Combination
NCT03380130	Y-90	Nivolumab	Sequential
NCT03033446	Y-90	Nivolumab	Combination
NCT03099564	Y-90	Pembrolizumab	Combination
NCT03259867	TATE	Nivolumab or pembrolizumab	Combination
NCT01853618	TACE or ablation	Tremelimumab	Combination
NCT03937830	TAE	Durvalumab and bevacizumab	Combination

Modified from: Singh et al.[101]

CA: cryoablation; DEB-TACE: Drug-eluting bead transarterial chemoembolization; RFA: radiofrequency ablation; SBRT: stereotactic body radiotherapy; TACE: transarterial chemoembolization; TAE: transarterial embolization; TATE: transarterial tirapazamine embolization; Y-90: radioembolization with yttrium-90.

months vs. 4.9 months, respectively, $p = 0.77$). With respect to radiologic progression-free survival, the statistically significant result was favorable for SOR, with 5.5 months vs. 2.8 months for the placebo group (HR 0.58, 95% CI 0.45—0.74; $p < 0.001$). Tumor response determined by RECIST was low: partial response in 2% of the SOR group vs. 1% of the placebo group, and neither group had complete response. The tumor control rate was statistically higher for SOR vs. placebo (43% vs. 32%; $p = 0.002$). Adverse effects were more frequent with SOR and included diarrhea, weight loss, hand-foot syndrome, alopecia, anorexia, and voice changes ($p < 0.001$). There were no grade 4 toxic events. The main reasons for toxicity associated with treatment interruption were gastrointestinal effects (5%), fatigue (4%), and liver function deterioration (5%). Dose had to be reduced in 26% of the patients and treatment was definitively interrupted due to intolerance in 44%. The results of another phase III study on an Asian population, which had a similar design to the SHARP study, showed a significant increase in overall survival in favor of SOR, but was numerically lower than that of the SHARP study (6.5 vs. 4.2 months, HR 0.68, 95% CI 0.5—0.93; $p = 0.14$)[108]. The difference in design of the Asian study included a 2:1 randomization, no primary aim was established, and the population was smaller ($n = 226$). The time to progression in that study was 2.8 months (2.63–3.58) in the SOR group, compared with 1.4 months in the placebo group (HR 0.57, 95% CI 0.42—0.79; $p = 0.0005$). The less favorable survival results can be related to the higher number of patients with hepatitis B virus (HBV), compared with the SHARP population (70.7% vs. 10.7%), a condition described as the least favorable for response to SOR[109]. The Asian study also had a higher number of patients with extrahepatic disease and elevated AFP, elements that have been associated with a poor response to SOR[109].

In the period after 2008, an increase in overall survival has been observed with SOR, in comparing the Western region analyzed in the SHARP pivot study (10.7 months in 2008 to 15.1 months in 2013) and the Asian region (from 6.5 months to 11 months). That effect is most likely the consequence of several factors: better patient selection criteria, better quality of SOR management after years of experience, and better second-line treatment options[110].

LEN is another multikinase inhibitor that acts on VEGFR-1, 2, and 3, fibroblast growth factor receptor-1, 2, 3, and 4, alpha-PDGFR, RET, and KIT. It was evaluated in the phase III REFLECT study vs. SOR as the control group and approved as first-line treatment in 2018. The primary aim of the pivot study included noninferiority (vs. SOR) in overall survival with a limit[111]. A total of 954 patients with unresectable advanced HCC were analyzed, but the population was selected with better characteristics than in the SHARP study. The cases were exclusively Child-Pugh class A, and patients with large tumor burden (>50% of liver involvement) and those with bile duct or portal vein invasion were excluded. The dose of LEN was calculated, based on body weight: 8 mg for subjects <60 kg and 12 mg for those ≥60 kg. The primary endpoint of noninferiority was met, with a HR of 0.92 (95% CI 0.79–1.06) and mean overall survival of 13.6 months for LEN vs. 12.3 months for SOR. Overall survival efficacy was greater in patients with baseline AFP levels ≥200 ng/mL (HR 0.78, 95% IC 0.63—0.98) and LEN was equally as effective as SOR in relation to other unfavorable factors, such as macrovascular invasion or extrahepatic involvement, as was the case in the Western patients. The goals of progression-free survival and tumor response were significantly better for LEN. More patients had a toxicity grade ≥3 (57% vs. 49%), as well as severe adverse events (18% vs. 10%) with LEN. The most common effects were high blood pressure (42% vs. 30%), diarrhea, reduced appetite, and weight loss. Quality of life parameters, particularly those related to functional capacity, pain, diarrhea, nutrition, and body image decreased more rapidly in the SOR group. A relevant result with LEN was that the overall tumor response was 18.8% (<1% complete response and 18% partial response) vs. 6.5% in patients with SOR (<1% complete response and 6.5% partial response). At the 2021 annual congress of the American Society of Clinical Oncology (ASCO) a *post hoc* analysis was presented that demonstrated the safety of LEN in patients that progressed to Child-Pugh class B in the phase III REFLECT study. The patients that suffered deterioration of liver function during treatment could continue receiving LEN[112] and it is included in the Mexican *CENETEC* guidelines as first-line management[113].

Atezolizumab plus bevacizumab. Multiple intrinsic mechanisms of immune pathway evasion, including the overexpression of VEGFs have been described in the genesis and progression of HCC. Thus, drugs with antiangiogenic action that reduce said immunosuppression mechanism within the tumor microenvironment favor the action of the anti-PD-1 and anti-PDL-1 drugs, by reversing immunosuppression through the VEGFs[114]. Atezolizumab is an anti-PD-L1 monoclonal antibody of the immunotherapy group and prevents the interaction of the PD-1 and B7-1 receptors, improving antitumor immunity[115]. Bevacizumab is a monoclonal antibody that binds to and neutralizes VEGF, thus inhibiting angiogenesis and tumor growth[116]. The combination of atezolizumab + bevacizumab (A + B) was initially evaluated in the phase Ib GO30140 study[117] and the combination was later compared with standard SOR treatment in the phase III IMbrave150 study[118]. The combination was approved by the FDA in May 2020 for the first-line treatment of unresectable HCC. The GO30140 study (phase Ib, multicohort) initially included 2 HCC cohorts for A + B. The first cohort was made up of 104 patients and a single treatment group and the second cohort was made up of 119 cases that were randomized for treatment with atezolizumab 1200 mg + bevacizumab 15 mg/kg IV every 3 weeks vs. atezolizumab alone. For the single treatment group, objective tumor response was 36%, including complete responses in 12% of patients, and in that scenario the primary aim was met at 12.4 months of follow-up. At the time of the first analysis, the mean response duration had not been reached (95% CI 11.9 months–not achieved), but the mean progression-free survival was 7.3 months (95% CI 5.4–9.9 months). With respect to safety, the grade 3–4 toxicity most commonly reported was high blood pressure (13%) and proteinuria (7%). However, 24% of the patients presented with severe adverse events, with deaths associated with liver function deterioration and pneumonitis in 3%[117]. In the study of the comparative cohort, follow-up was 6.7 months, with a progression-free survival of 5.6 months (95% CI 3.6–7.4 months) for the A + B group vs. 3.4 months (95% CI 1.9–5.2 months) for the group with atezolizumab alone (HR 0.55; p = 0.011). The objective responses were 20% (complete in 2%) vs. 17% (complete in

5%) and stable disease in 47% vs. 32%, respectively. It should be emphasized that none of the groups reached the mean response duration. For the A + B combination group, the most frequent grade 3–4 adverse effects were high blood pressure (5%) and proteinuria (3%) and 12% of the patients presented with severe adverse events[117].

The IMbrave150 study[118] included 501 patients with unresectable or metastatic HCC, with ECOG performance status 0–1, Child-Pugh class A, and no coinfection with hepatitis B or C. They were randomly assigned in a 2:1 ratio to receive first-line treatment with A + B vs. standard therapy with SOR. Overall survival at 12 months was 67.2% (95% CI 61.3–73.1) for the A + B combination, compared with 54.6% (95% CI 45.2–64.0) for SOR. Median progression-free survival was 6.8 months (95% CI 5.7–8.3) and 4.3 months (95% CI 4.0–5.6), respectively, with a HR for disease progression or death of 0.59 (95% CI 0.47—0.76; $p < 0.001$). A total of 56.5% of the patients in the A + B arm presented with grade 3–4 adverse events (15.2% presented with high blood pressure) and 55.1% in the SOR group. Overall tumor response measured by RECIST 1.1 was 28% (95% CI 23–33) in the A + B arm and 12% (95% CI 7–17) in the SOR group ($p < 0.0001$). The overall response evaluated through mRECIST was 33% (95% CI 28–39) vs. 13% (95% CI 8–19), respectively ($p < 0.0001$)[118].

Those results are relevant, given that they are the first to demonstrate superiority in combination immunotherapy programs over standard therapy, prolonging overall survival, together with deep and lasting tumor responses, even including complete tumor remission. All of the above supports the new combination treatment proposals as the best first-line alternative for advanced HCC, even above SOR (considered standard therapy for 10 years).

44. The second-line choice (category 1) is based on tumor characteristics, liver reserve, the performance status of the individual, and the first-line medication that resulted in failure due to progression or intolerance.

In complete agreement: 92%; in partial agreement: 8%.

The presence of portal invasion, extrahepatic extension, liver function status (Child-Pugh score), and preferably, preserved liver function (ECOG performance status 1–2) should be evaluated in the treatment of advanced disease[85,105]. Treatment prior to tumor progression or treatment intolerance should also be considered. The presence of liver decompensation (jaundice, variceal bleeding, encephalopathy, or ascites) or Child-Pugh class C should be a contraindication for any therapy that could produce greater liver injury[105].

45. The accepted second-line therapies in advanced HCC (category 1) are regorafenib, cabozantinib, and ramucirumab.

In complete agreement: 91.67%; in partial agreement: 4.17%; in complete disagreement: 4.17%.

Category 1 drugs are: regorafenib, cabozantinib, and ramucirumab.

Regorafenib. Regorafenib is an oral multikinase inhibitor that is very similar to SOR. The RESORCE pivot study[119] showed an increase in mean overall survival, when comparing regorafenib with placebo in 573 individuals (10.6 vs. 7.8 months, respectively) that progressed on SOR (but tolerated it) and had Child-Pugh class A liver function (HR 0.63, 95% CI 0.50—0.79; $p < 0.001$). There was also benefit in progression-free survival (HR 0.46, 95% CI 0.37—0.56; $p < 0.001$), time to progression (HR 0.44, 95% CI 0.36—0.55; $p < 0.001$), objective response (11% vs. 4%; $p = 0.005$), and disease control (65% vs. 36%; $p < 0.001$). Those results enabled its approval as a second-line treatment in individuals with tumor progression on SOR, but that tolerated the drug.

Cabozantinib. Another multikinase inhibitor, cabozantinib inhibits VEGFR 1-3, MET, and AXL. The CELESTIAL study[120] included 707 individuals with Child-Pugh class A advanced HCC, with progression on SOR, and showed a median overall survival of 10.2 months with cabozantinib vs. 8 months with placebo and a median progression-free survival of 5.2 months and 1.9 months, respectively (HR 0.76, 95% CI 0.63—0.92; $p = 0.005$ for overall survival and HR 0.44, 95% CI 0.36—0.52; $p < 0.001$ for disease progression).

Ramucirumab. Ramucirumab is a monoclonal antibody that targets VEGFR-2. The phase III REACH-2 study[121] showed improved median overall survival and progression-free survival in patients treated with ramucirumab, compared with the placebo group, with 8.5 months vs. 7.3 months (HR 0.71, 95% CI 0.53—0.95; $p = 0.20$) and 2.8 months vs. 1.6 months (HR 0.45, 95% CI 0.34—0.60; $p < 0.001$), respectively. A later analysis between the REACH-1 and REACH-2 studies showed an increase in median survival for the patients treated with ramucirumab (8.1 months) vs. placebo (5.0 months) (HR 0.69, 95% CI 0.57—0.84; $p < 0.001$), in the subgroup of patients with a baseline AFP level $\geq$400 ng/mL. It is the first drug to be approved, based on response determined by a baseline biomarker (AFP).

46. Immunotherapy is a category 2A treatment option (nivolumab ± ipilimumab), whereas pembrolizumab is category 2B.

In complete agreement: 91.67%; in partial agreement: 8.33%.

Nivolumab. Nivolumab is an anti-PD-1 antibody and category 2A treatment option. It is the first immunotherapy drug to be approved for use in HCC and is indicated in patients with Child-Pugh class A liver function. The phase I/II CheckMate 040 study[122] that included 262 patients showed objective response in 20% and disease control in 64%. The patients in the dose expansion phase that progressed on SOR and did not have viral hepatitis achieved a mean overall survival of 13.2 months and a 6-month survival of 75%. In addition, the median response duration was 17 months for patients not exposed to SOR and 19 months for those treated with SOR.

Nivolumab plus ipilimumab. Ipilimumab is an antibody that targets cytotoxic T lymphocyte-associated antigen 4 (anti-CTLA-4), and so the combination includes two checkpoint inhibitors with different inhibition points. It is a category 2A option indicated in Child-Pugh class A liver disease and was evaluated in patients with advanced HCC that were previously treated with SOR[123]. A total of 148 individuals with advanced HCC were randomized into one of 3 groups. Group A ($n = 50$) was treated with nivolumab 1 mg/kg and ipilimumab 3 mg/kg × 4 doses every 3 weeks, followed by nivolumab 240 mg IV every 2 weeks. Groups B and C received the same drugs at different doses and durations. The group A results are shown here, given that they enabled the treatment's approval as second-line therapy. The mean age of the patients was 60 years, 86% were men, 86% had BCLC C, 100% Child-Pugh class A, 36% vascular invasion, 80% extrahepatic disease, 50% AFP > 400 ng/mL, 56%

HBV etiology, and 14% HCV etiology. The overall response rate determined through RECIST v1.1 was 32%. Complete response was 8%, partial response was 24%, disease was stable in 18% of patients, and disease progressed in 40%. Mean follow-up to the last cutoff point was 30.7 months and definitive response duration for the group had not been reached. Phase III of the study is currently being developed.

Pembrolizumab. A category 2B option, pembrolizumab is an anti-PD-1 antibody and is indicated in patients with Child-Pugh class A. It was evaluated in patients that were previously treated with SOR or that did not tolerate SOR in the phase II KEYNOTE-224 study[124,125]. In the 413 patients included, there was objective response in 17% and stable disease in 44%, whereas 33% progressed with an unreached median response duration at the time of publication, resulting in the FDA approving the treatment as second-line therapy. However, the phase III KEYNOTE-240[125] that compared second-line pembrolizumab vs. placebo did not achieve the primary endpoints, regarding overall survival and progression-free survival.

Given the rapid development of those treatments, their best sequence is still to be determined. According to the 2020 National Comprehensive Cancer Network (NCCN) version 5 guidelines (available at: nccn.org), SOR can be used in patients with tumor progression, or after using LEN, with Child-Pugh class A or B liver reserve, up to 7 points. There is no information on the use of LEN in patients with progression on SOR.

47. The double blockage of immune system checkpoints (anti-PD1/PDL1 and anti-CTL4) is a therapeutic strategy being studied as first-line treatment, showing promising results in BCLC C HCC.

In complete agreement: 100%.

Tremelimumab plus durvalumab. The combination of tremelimumab (anti-CTLA-4) + durvalumab (anti-PD-L1)[126] was evaluated in a phase I/II clinical trial, with the administration of tremelimumab 300 mg × 1 dose plus durvalumab 1500 mg every 4 weeks ($n = 75$). The study patients had a median age of 66 years, 86% were men, 57% had been previously treated with SOR, 16% presented with intolerance, and 27% rejected its use. Liver function stage was Child-Pugh class A (5 points) in 68%, Child-Pugh class A (6 points) in 31%, and Child-Pugh class B (7 points) in 1.3%. According to the BCLC classification, 1.3% had BCLC A, 17.3% had BCLC B, and 77.3% had BCLC C. The most frequent etiologies were HBV (36%) and HCV (28%). Twenty-one percent of the patients presented with vascular invasion and 70% had extrahepatic spread. AFP levels were above 400 ng/mL in 46.7% of the population. The objective response rate was 24%, there was complete response in 22.7% of the patients and stable disease in 21.3%. The median disease-free survival was 1.86 months, and the median overall survival was 18.73 months. The phase III HIMALAYA study is currently evaluating combined immune checkpoint inhibition in the first-line treatment of advanced HCC.

LEN plus pembrolizumab. In a phase Ib study conducted on 104 patients with advanced HCC and compensated liver disease, the potential synergy of different mechanisms of action for first-line treatment was evaluated, utilizing the combination of LEN (a multikinase inhibitor) and pembrolizumab (immunotherapy)[127]. The median age of the patients was 66 years, 81% were men, 71% had BCLC C and the rest had BCLC B, and 30% had AFP levels above 400 ng/mL. In relation to liver reserve, 71% of the patients had Child-Pugh class A (5 points), 27% had Child-Pugh class A (6 points), and 2% had Child-Pugh class B (7 points). Response was evaluated through RECIST and the overall response rate was 36%, with complete response in 1%, and partial response in 35%. Disease was stable in 52% of the patients, whereas 7% had tumor progression. When response was evaluated through mRECIST, overall response was 46%, with complete response in 11% and partial response in 35%. Disease was stable in 42%, and 7% presented with disease progression. The median of response duration determined by RECIST was 12.6 months, and by mRECIST, was 8.6 months. The median progression-free survival through RECIST was 9.3 months and by mRECIST was 8.6 months, and the median overall survival was 22 months. At present, the strategy is being evaluated in the phase III LEAP-002 study. The preliminary results of the combination are very promising and strengthen the interest in the combination of antiangiogenic therapy and immunotherapy.

48. In patients with terminal HCC and a life-expectancy of 3–4 months, management is multidisciplinary and complication-related.

In complete agreement: 100%.

In countries such as Mexico, diagnoses are still frequently made at advanced stages of the disease, in which the performance status and/or liver function of the patient prevents any type of treatment from being offered, regardless of the tumor characteristics. That was demonstrated in a recent study that analyzed the stage at diagnosis of liver tumors in patients treated at the *Hospital Universitario Dr. José Eleuterio González* of the *Universidad Autónoma de Nuevo León* within the time frame of 2012 to 2018[128]. Stage at diagnosis was compared in patients diagnosed with HCC and/or cholangiocarcinoma at the Hepatology Center vs. patients diagnosed at the University Center Against Cancer of the same hospital, finding that of the 109 patients evaluated, 93% ($n = 102$) had cirrhosis of the liver. Ninety-four patients had HCC, 55 of whom were diagnosed at the hepatology center and 39 at the cancer center. Those authors reported that 31 and 51% of the patients diagnosed met the Milan criteria or the UCSF criteria, respectively, whereas only 12 and 23% at the cancer center could be candidates for curative treatment, i.e., liver transplantation.

Moreover, HCC can accelerate the course of any stage of cirrhosis, but especially of decompensated cirrhosis, which is why patients are frequently found with said deterioration. Therefore, it is recommended to give pertinent management to the most frequent complications, such as ascites, refractory ascites, hydrothorax, gastrointestinal bleeding, infections, and hepatic encephalopathy, among others. It is also recommended to form multidisciplinary care teams to educate and guide the patients, caregivers, and treating physicians, to optimize care and the adherence to guidelines on the management of complications of liver cirrhosis. Care by the multidisciplinary team also includes the management of anorexia, fatigue, nausea/vomiting, pruritus, and constipation[129–133]. When the tumor causes bile duct compression, with its consequent obstructive complications, deviation through the endoscopic or percutaneous placement of a stent can be a management option. In addition,

management involves the treatment of metastases, keeping in mind that the most frequent sites are the lungs, lymph nodes, and bones. Palliative radiotherapy is indicated for metastases to the lymph nodes, bones, brain, and other sites. Bone metastases cause pain and fracture. Radiotherapy can be utilized to alleviate pain in patients with bone metastases and relieve the symptoms of lung or lymph node metastases, as well[132].

49. Patients with advanced HCC should receive better symptomatic and palliative support at diagnosis, with respect to pain control, nutrition, and psychosocial support.

In complete agreement: 95.83%; in partial agreement: 4.17%.

Providing symptomatic support and palliative care is recommended to all patients with HCC, within 8 weeks after diagnosis, given that curative options are limited and the progression of the disease causes anxiety and uncertainty in the patient and his/her family, with respect to diagnostic and treatment decisions. Older adults are more affected by HCC due to numerous comorbidities and to the complexity of the disease. That population, in particular, would greatly benefit from having access to palliative care and symptomatic support services throughout the course of the disease[134].

Comprehensive interdisciplinary evaluation for the patient and his/her family, that includes hepatologists, oncologists, oncologic surgeons, and surgeons that perform palliative procedures, is the basis for developing an individualized plan[135,136]. Continuous symptom evaluation enables the care plan to be adjusted to anticipate, prevent, and treat the physical, psychologic, social, and spiritual needs of the patient. Coordinating those aspects at the different levels of care is important[137].

Palliative care prevents, identifies, and evaluates the symptoms, implementing the treatment of pain and other physical, psychologic, and spiritual problems. In the context of underlying liver disease, that population can experience symptoms of end-stage liver disease, as well as of HCC. The most frequent symptoms are those related to chronic liver disease (ascites, encephalopathy, jaundice, variceal bleeding, abdominal pain, weight loss). Dyspnea, cachexia, anorexia, and vomiting, among others, are also frequent, and they derive from both liver disease evolution and tumor progression[132–137].

With respect to the palliative model, it is essential to evaluate the symptomatic complexity of the patient in the following 7 basic aspects:

Physical symptoms: abdominal pain, nausea/vomiting, anorexia, low weight, dyspnea, fatigue, diarrhea, obstructive symptoms, and encephalopathy.

Psychologic and psychiatric symptoms: anxiety, depression, insomnia, delirium, desire to hasten death, and decision-making capacity.

Social, spiritual, religious, and existential aspects: guilt, anger, despair, loss of family role, loss of work, loss of faith.

Cultural aspects: understanding of the disease, decision-making, fear of being a burden, fear of death, loss of dignity.

Daily care: costs, transfers, hospitalizations, polypharmacy, geriatric syndromes, and comorbidities.

End-of-life care: palliative sedation will be required with place of death at the hospital or at home.

Ethical and legal aspects: advance directives, pensions, retirements, adoptions, and incapacities[135].

We emphasize that patients with HCC should be referred to palliative care early on, not excluding patients that receive disease-modifying treatment or transplantations, given that there are reports showing improved quality of life through symptom control, as well as increased survival[135–137].

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Conflict of interest

LECG declared having collaborated with BMS, Exelixis, Viking, Madrigal, Novonordisk, Avant Santé, Cellpharma, and Gilead.

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ERG declared having collaborated with MSD, Sanofi/Aventis, Roche/Genentech, AMGEN, and Bay.

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