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Bland Embolization and Transarterial Chemoembolization in Hepatocarcinoma

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Abstract

Hepatocarcinoma (HCC) is the main cause of morbidity and mortality worldwide in patients with cirrhosis. Eighty percent of cases worldwide are due to infections with hepatitis B and C viruses, but nonalcoholic steatohepatitis (NASH) is projected to be an important etiology. It is usually diagnosed in advanced stages, only 15% of patients are surgical candidates, and up to 35% can receive only supportive care. This pathology has changed over time with the significant advances in treatment alternatives that can improve life expectancy for patients who are not surgical candidates. Therapeutic alternatives are available based on staging according to different models and the Barcelona Clinic Liver Cancer (BCLC) staging system. Systemic pharmacological options (neoadjuvant, adjuvant, and hormonal therapy), surgical options, and locoregional therapies have been developed; all these interventions have been directed to increase the life expectancy of some patients with variable results. Regional therapies include transarterial embolization (TAE) or bland embolization, transarterial infusion chemotherapy, conventional transarterial chemoembolization (TACE), drug-eluting bead transarterial chemoembolization (DEB-TACE), and transarterial radioembolization, with no substantial difference in outcomes between patients treated with TACE and those receiving DEB-TACE, but benefits of lower systemic adverse effects and improved of quality-adjusted life years measure with DEB-TACE. With the addition of immunotherapy to these interventions, the outcomes are expected to be even more impactful on main outcomes such as survival and disease-free survival.

Keywords
- hepatocellular carcinoma
- therapeutic embolization
- intra-arterial injections
- hepatic cirrhosis
- sorafenib

Hepatocarcinoma (HCC) is the main cause of mortality and morbidity worldwide. By 2020 liver cancer was the sixth leading cause of cancer, accounting for 5% of all cancers.[1] In Latin America, there are special considerations regarding epidemiology and outcomes, this in part due to the economic, sociocultural heterogeneity, and geographic disparities in healthcare services where the surveillance programs and therapeutic options are difficult.[2]

Eighty percent of the HCC cases worldwide are related to infection with hepatitis B and C viruses, but there are regions of Latin America where hepatitis C infection and alcoholic cirrhosis predominate, as is the case of Argentina. In

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comparison, hepatitis B is the main cause of HCC in Brazil.[3,4] Transition in the etiology has been occurring in Western countries, with an increase in the incidence of HCC related to NASH and decrease in viral etiology.[5,6] Due to this epidemiological change, increases in the prevalence and incidence of chronic liver disease are projected.[7,8] Unfortunately HCC is usually diagnosed in advanced stages, only 15% of patients are surgical candidates, and up to 35% can receive only supportive care at the time of diagnosis.[9]

Different therapeutic alternatives (►**Fig. 1**) are available and are based mainly on lesion characteristics, clinical features, laboratory features, and the presence of metastasis. Different validated classification and staging models have been developed to define the therapeutic approach (►**Table 1**).[10]

There are many treatment options available for HCC, including pharmacologic (neoadjuvant, adjuvant, and hormonal therapies),[11,12] surgical,[13,14] and locoregional[15–18] therapies.[9] These therapies have been reported to increased survival by 20 to 30 months in patients with intermediate-stage tumors and from 10 to 19 months in patients with intermediate-stage tumors and advanced-stage tumors with preserved liver function, respectively. These interventions have overall improved the outcomes of HCC patients,[19,20] and different scientific societies have made great efforts unifying concepts and offering diagnostic and therapeutic guidelines. Latin America even has participated in this endeavor through the Mexican, Argentine, and the LAASL guidelines.[21]

This review will discuss the different modalities of locoregional therapies, including their origins and evolutions, variables involved in achieving therapeutic success, and how the inclusion criteria has changed overtime, different classification and staging systems that support decision-making in different stages of management, and the available evidence comparing different locoregional therapies and introducing up-and-coming combination therapies with systemic immunotherapy.

Regional Therapy

Regional therapies correspond to transarterial interventions directed to palliative care and are offered to patients with intermediate stages of multinodular disease without extrahepatic metastasis who have sufficient functional hepatic reserve (see ►**Fig. 2**).[24] These treatments differ from ablative therapies that are considered therapies with curative potential for small HCC lesions (usually smaller than 3–4 cm), up to three lesions and tumors that are approachable guided by imaging; however, this intervention is usually added to surgical resection and/or liver transplantation.[25] Regional therapies include transarterial embolization (TAE), intra-arterial chemotherapy (IAC), transarterial chemoembolization (TACE; see ►**Fig. 3**), drug-eluting bead transarterial chemoembolization (DEB-TACE; see ►**Figs. 4**–**6**), and trans-arterial radioembolization (TARE; see ►**Fig. 1**).[25,26]

The fundamental principle of embolization therapy is the induction of ischemia and tumor necrosis by occluding the feeding arteries of the lesion. Although 20 to 25% of the blood supply of the liver is provided by the hepatic artery and 75 to 80% is provided by the portal route,[27] this neoangiogenesis and predominance of the hepatic arterial system begins to occur from the high-grade dysplastic nodule and ends in the moderately differentiated HCC,[28] facilitating the use of vascular occlusion techniques with or without drugs or radiopharmaceuticals in the management of hepatic lesions such as HCCs.

TACE consists of injecting chemotherapeutic drugs with or without lipiodol into the hepatic artery followed by the injection of embolizing agents, while DEB-TACE consists of infusing microspheres loaded with chemotherapeutic agents, allowing sustained delivery of the drug, followed by embolization therapy. TARE is the infusion of radiopharmaceutical analogs of TACE in which microspheres loaded with yttrium-90 are deposited in the tumor tissue to achieve localized β-radiation, followed by embolization.

The Origin, Evolution of the Effectiveness, and Current Indications

Chemoembolization was established as standard of treatment in the intermediate stage of HCC. In 2002, Lo et al[29] and Llovet et al[30] presented the results of their clinical trials. The first was a randomized controlled study that evaluated the efficacy of TACE with lipiodol plus cisplatin and gelatin sponge particles injected through the hepatic artery versus symptomatic treatment in patients with unresectable HCC (40 patients and 40 controls). In this study, significantly longer survival ($p = 0.002$) was achieved in the chemoembolization group at 1 year (57 vs. 32%), 2 years (31 vs. 11%), and 3 years (26 vs. 3%) than in the control group, respectively. After adjusting for baseline variables of the patients, a survival benefit was observed in patients undergoing chemoembolization, with a death risk ratio (RR) of 0.49 (95% confidence interval [CI]: 0.29–0.81; $p = 0.006$). In Llovet et al's trial,[30] patients with unresectable HCC with Child-Pugh A or B and Okuda stage I or II who did not undergo curative management were randomized to receive one of three interventions, repeated treatment with arterial embolization with gelatin sponges, or chemoembolization using gelatin sponges with doxorubicin or none. Thirty-seven patients were assigned to the arterial embolization group, 40 to the chemoembolization group, and 35 to the control group. Probability of survival at 1 and 2 years was 75 and 50% for the embolization group, 82 and 63% for the chemoembolization group, and 63 and 27% for the control group, respectively. Chemoembolization was statistically superior to the control group ($p = 0.009$) and survival benefit was obtained with hazard ratio (HR) for death of 0.47 (95% CI: 0.25–0.91, $p = 0.025$). A systematic review was published the year after these articles were released, and it concluded that chemoembolization/embolization improves survival of patients with unresectable HCC (OR: 0.53; 95% CI: 0.32–0.89; $p = 0.017$); so, these treatments might become the standard of treatment.[31] In fact, nowadays there are multiple publications of scientific societies and different guidelines

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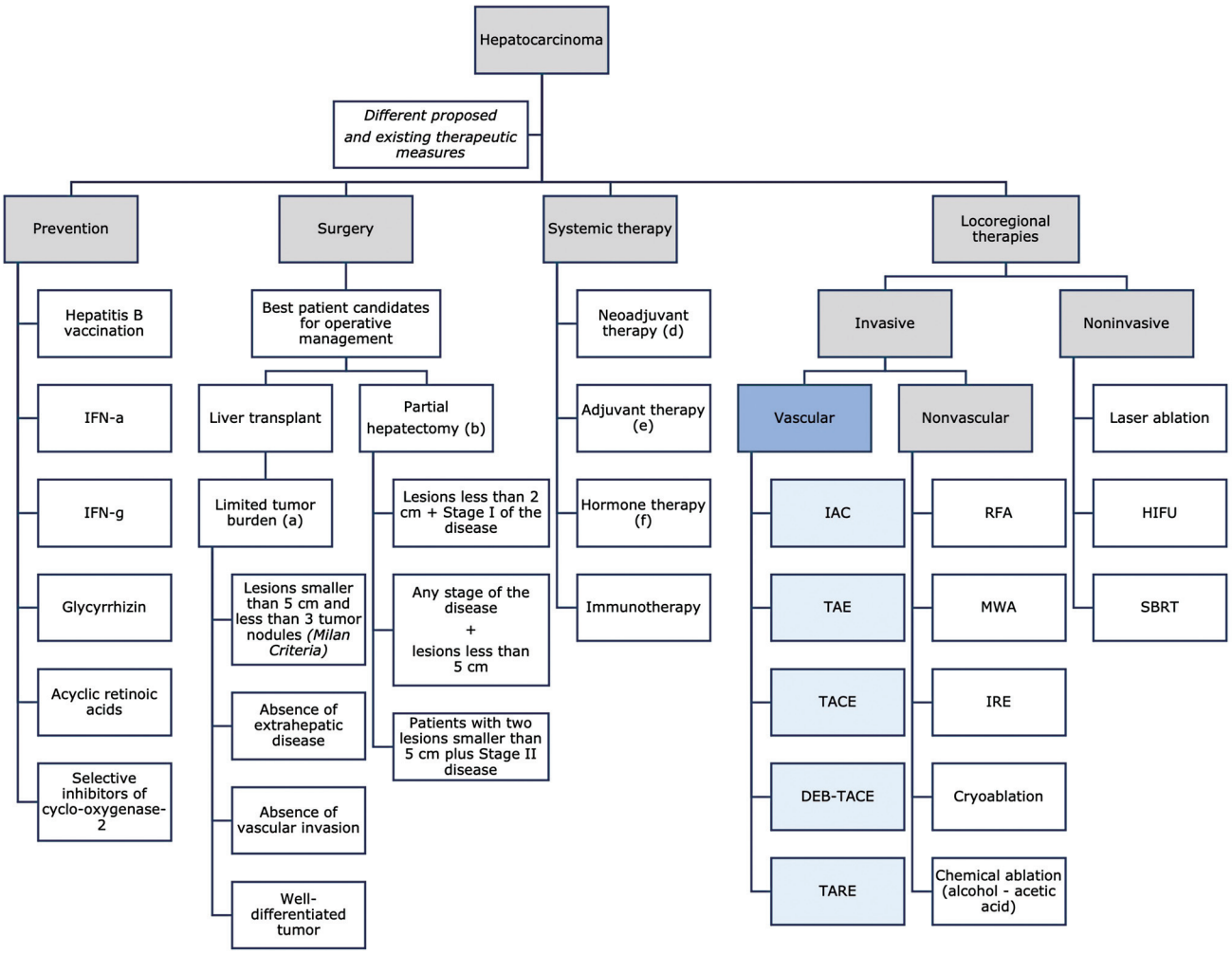

Fig. 1 Therapeutic options available for patients diagnosed with HCC. **Prevention—IFN-a:** useful in patients with chronic hepatitis or cirrhosis of viral origin; it can modulate liver inflammation, necrosis, and subsequent regeneration, leading to malignant transformation and the suppression of tumor cell growth by inducing cell cycle arrest and apoptosis. **IFN-g:** restores the alters the presentation of antigens from tumor cells, restoring their sensitivity to CTLs. **Glycyrrhizin:** licorice root extract, cortisone-like structure, exerts a suppressive effect on liver inflammation, and inhibits liver cirrhosis. **Acyclic retinoic acids:** inhibit the development of hepatocarcinoma in animal models by inducing apoptosis. The absence or decreased levels of retinoic acid is hepatocarcinogenic. **Selective inhibitors of cyclo-oxygenase-2 (Cox-2):** Cox-2 overexpression has been shown to produce hepatocarcinoma, and researchers are currently assessing whether its inhibition is a protective factor. **Surgery:** The variables described are for the definition of liver transplantation. An improvement in survival up to 61% at 5 years has been reported; the main advantage of liver transplantation is that it avoids therapeutic failure with other surgical modalities such as hepatectomy or ablative treatments, including local recurrence and the development of metachronic tumors. However, donors are limited. (**a**) Present all the following conditions; (**b**) present at least one of the following conditions. **Systemic therapy:** ***First-line neoadjuvant therapies*** (**d**) are tyrosine kinase inhibitors and VEGF inhibitors such as sorafenib, sunitinib, brivanib, linifanib, erlotinib, doxorubicin, and lenvatinib. Likewise, in patients with HCC with the etiology of hepatotropic viruses such as hepatitis B and hepatitis C, management with antivirals is provided as neoadjuvant therapy and is considered part of the multidisciplinary treatment. It is associated with less vascular invasion, decreased recurrence and morbidity rates, and greater recovery of liver function in patients with HCC related to hepatitis B. ***Adjuvant therapy*** (**e**) including ***hormone therapy*** (**f**)**:** includes management with antiviral therapy such as pegylated IFN, ribavirin, nonstructural (NS) protein 3/4A protease inhibitors, NS5A complex inhibitors, NS5B nucleotide polymerase inhibitors, NS5B non-nucleotide polymerase inhibitors, nucleoside analogs, as well as tyrosine kinase inhibitors such as sorafenib and immunotherapy with drugs, such as cytokine-induced killer cell inducers, NK cells and cytokine-induced killer T cells, and monoclonal antibodies such as nivolumab, among others. **Locoregional therapies:** The vascular therapies that are part of the invasive locoregional interventions that this review describes are indicated in blue. IAC, intra-arterial chemotherapy; TAE, transarterial embolization; TACE, transarterial chemoembolization; DEB-TACE, drug-eluting bead transarterial chemoembolization; TARE, transarterial radioembolization; RFA, radiofrequency ablation; MWA, microwave ablation; IRE, irreversible electroporation; HIFU, high-intensity focal ultrasound; SBRT, stereotactic body radiation therapy.

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Table 1 Characteristics included in HCC staging systems

Staging system	Patient characteristics		Tumor characteristics						Liver functional status						
	Functional status[a]	Age	Size	Number	Portal invasion	Metastasis	Nodules	Alpha fetoprotein	Child–Pugh	Albumin	Serum bilirubin	Serum creatinine	PT/INR	Ascites	Alkaline phosphatase
BCLC (updated)	X		X	X	X	X			X	X	X		X	X	
Okuda			X							X	X			X	
CLIP			X		X			X	X	X	X		X	X	
HKLC	X		X	X	X	X			X	X	X		X	X	
Alberta Algorithm	X		X	X	X	X			X	X	X		X	X	
MESIAH scale		X	X	X	X	X		X		X	X	X	X		
GRETCH scale	X				X			X			X				X
CUPI			X			X	X	X			X			X	X
ITA.LI.CA	X		X	X	X	X		X	X	X	X		X	X	

Abbreviations: PT/INR, prothrombin time/international normalized ratio; CLIP, Cancer of the Liver Italian Program; BCLC, Barcelona Clinic Liver Cancer; GRETCH, Groupe d'Etude et de Traitement du Carcinome Hepatocellulaire; CUPI, Chinese University Prognostic Index; MESIAH, Model to Estimate Survival in Ambulatory HCC patients; HKLC, Hong Kong Liver Classification; ITA.LI.CA, Italian Liver Cancer.
Notes: Letter "X" indicates that the staging system uses the variable within its scoring system.
[a]The functional status is measured based on the **ECOG** (Eastern Cooperative Oncology Group) scale, the only scale among staging systems that uses a different scale is the **GRETCH** scale that uses the Karnofsky index.

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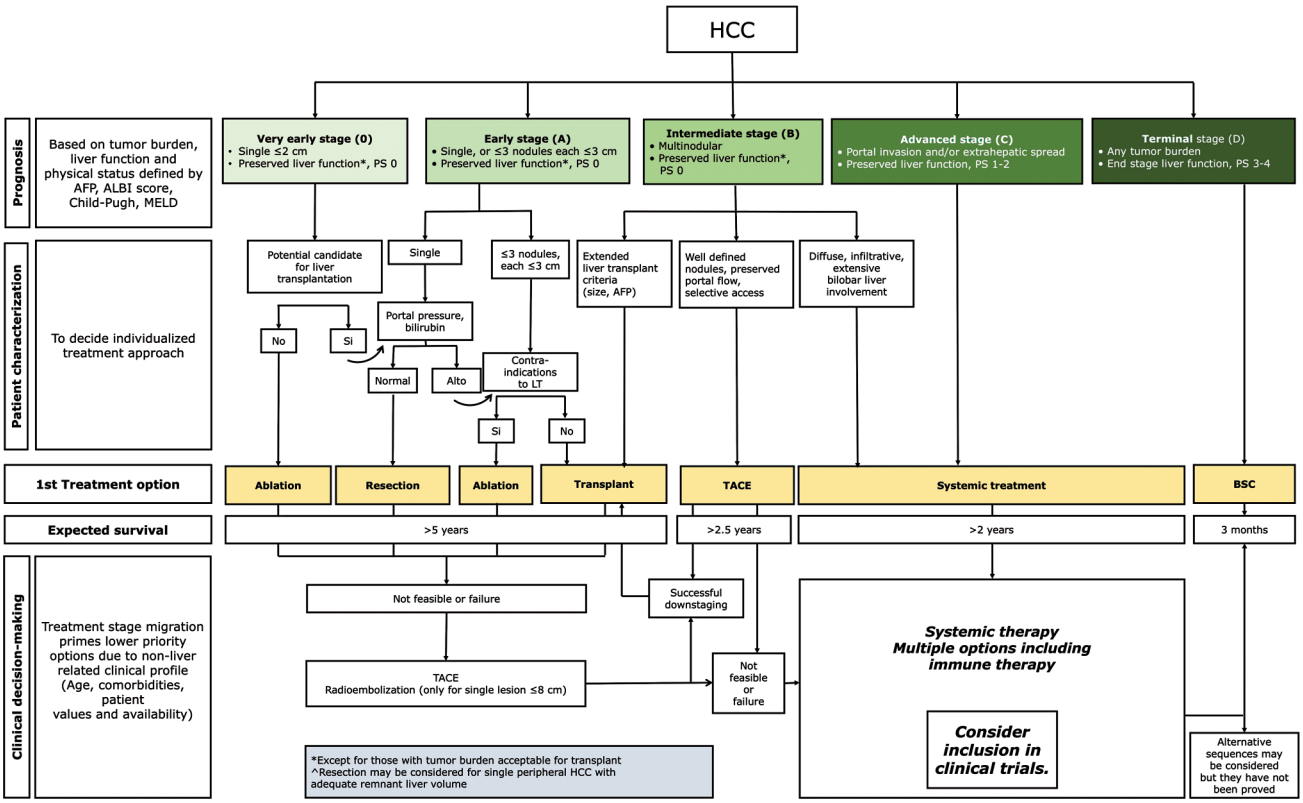

Fig. 2 Hepatocarcinoma staging system and therapeutic strategy (adapted from BCLC 2022).

about HCC treatments that had referenced chemoembolization as a therapeutic alternative, and there are guidelines that had established what patients are candidates to receive these therapies, what are exclusion criteria or contraindications, and what are the definitions for the failures of the transarterial interventions and refractoriness criteria.[21,32–35] These recommendations are summarized in ►**Table 2**.

The evolution of intra-arterial therapies has been the *extended criteria* to manage HCC; this concept includes the "*bridge-to-transplantation*" and "*downstaging*" therapies.[36] Accumulated experience with the *bridge-to-transplantation* therapy indicates that waiting time for candidates are prolonged, which are different for each region and locality but represent a big problem. Exit from waiting list has been recorded up to 25% at 6 months, 38% at 12 months, and up to 55.1% at 18 months, situations that might be reduced to 3 to 13% by providing TACE.[36] In addition, when we evaluated some patients undergoing "*bridge therapy with TACE*" in our series of 45 patients, a 1-year survival rate of 69%, a 2-year survival rate of 50%, and 3- and 4-year survival rates of 40% were observed. Complete response rate was 11.1 and 44.4% of patients achieved a partial response, 31.1% experienced progression, and 13.3% had a stable disease.[5] Other authors, such as Byrne and Rakela, have documented 5-year survival up to 93% with a tumor recurrence rate as low as 2%, and many of these patients may eventually receive a liver transplant.[37]

Data have shown success rates ranging from 24 to 90% for "*downstaging*" indication, what means restaging to a lower category. When comparing the survival of transplanted patients with those who did not receive a transplant but were given a downstaging treatment, no differences in mortality were observed.[38] Affonso et al examined a series of 200 patients and observed no difference in overall survival at 5 years after transplant between patients who underwent TACE with *downstaging* intention and those who underwent TACE as a *bridge-to-transplantation* therapy (73.5 vs. 74.8%; $p = 0.31$); the recurrence-free survival rate was 62.1% in the downstaging group in this study and 74.8% in the bridge therapy group ($p = 0.93$).[39]

Finally, transarterial therapies are considered as extended criterion indication for patients with advanced-stage HCC (BCLC C and D). These candidate patients represent slightly more than 50% of patients with HCC in some regions according to data from the multicentric and multinational BRIDGE registry that included 18,031.[40] The results sought for these patients are symptomatic improvement since they usually have an estimated survival of 3 months due to the severity of the disease.

Regarding published Latin American experiences, there are documents dating back to the 2000s where the first experiences with TACE in countries such as Chile,[41] Ecuador,[42] Guatemala,[43] Colombia,[44] Mexico,[45] and Brazil[46] were publication of case series and based their conclusions fundamentally on the feasibility of the technique, the low incidence of complications, its good tolerance, and the

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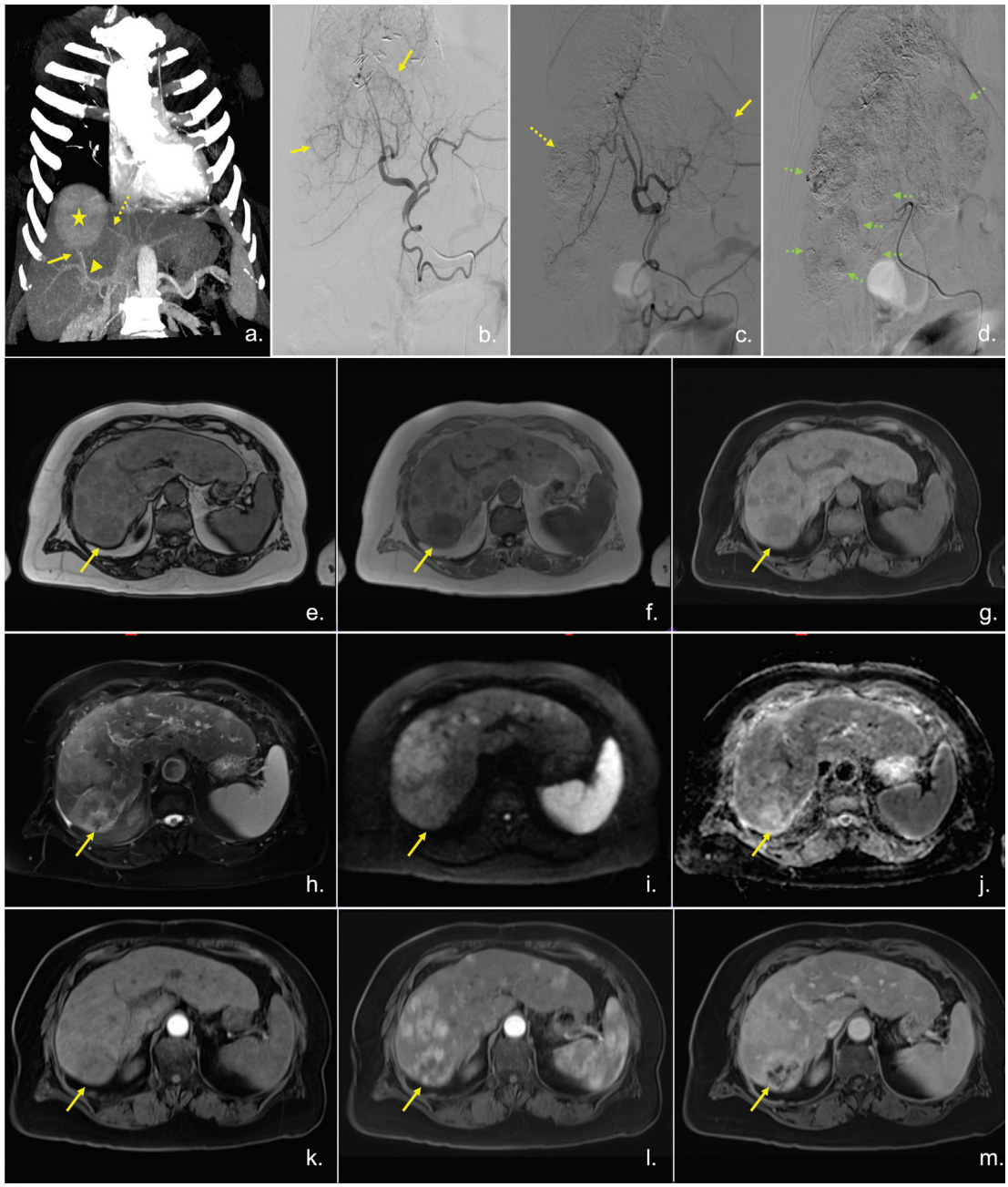

Fig. 3 A 77-year-old cirrhotic patient, Child–Pugh B—7 points, ECOG 2, BCLC-B, known multinodular HCC, previous partial hepatectomy, no esophageal varices, no ascites, no encephalopathy. Received management with TACE shown below but had poor response. In controls, it was documented deterioration of liver function without possibility of being considered for additional interventions and was candidate for management by palliative care. (**a**) In this last intra-arterial treatment only CT angiography was considered pre-TACE: arrowhead points out right branch of the hepatic artery. Interrupted arrow points out left portal middle branch. Asterisk marks out Hepatocellular carcinoma already known which had 7.6 cm of maximum diameter. (**b–d**) Three months later, TACE was scheduled: Catheterization and selective angiography of the right hepatic artery was done and multiple hypervascularized lesions of different sizes are defined. They infiltrate whole right hepatic parenchyma. Administration of mixed doxorubicin and lipiodol is performed until a decrease in the flow of the right arteries and opacification of the multiple nodules was obtained (green arrow in ***"d"*** picture points out embolized hepatocarcinoma lesions). (**b**) Arrows indicate vascularization that circumscribes neoplastic lesions. (**c**) Continuous arrow indicates a nonembolized lesion and the discontinuous arrow indicates an already embolized lesion. (**e–m**) Selected images in 2-month control MRI where multiple focal lesions of hepatocarcinoma were present. The lesion marked out with yellow arrow in each picture corresponds to the lesion pointed out with an asterisk in the picture **"a"** in the liver segment VII. mRECIST was not possible to be calculated because it was considered noncomparable pre- and post-TACE imaging modality (first was CT angiography and post-TACE it was MRI); therefore LI RADS was reported, which was considered ***LR-TR viable*** due to focal lesions in segment VII considered with findings of embolization and persistence of viable tumor and multiple not measurable lesions suggestive of hepatocarcinoma (**e:** T1 out of phase, **f:** T1 in phase, **g:** T1 fat sat, **h:** T2 fat sat, **i:** diffusion, **j:** ADC, **k:** early arterial phase, **l:** arterial phase, **m:** portal phase).

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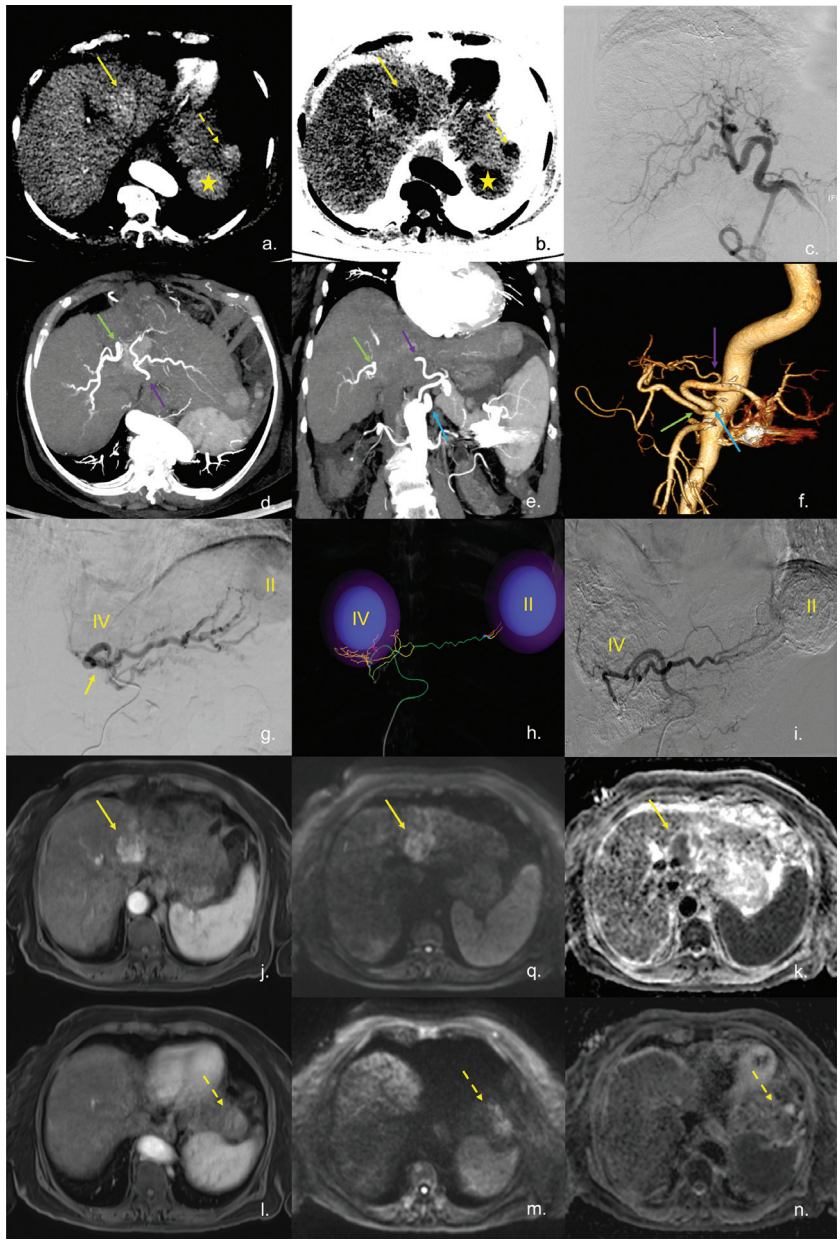

Fig. 4 A 72-year-old cirrhotic patient due to hepatitis C, multifocal hepatocarcinoma, Child–Pugh A—5 points, ECOG 0, BCLC B, in systemic including antiviral treatment, now with new lesions. Control tomography showed (**a, b**) lesions in liver segments II and IV consistent with known hepatocarcinoma; image **a** in conventional gray scale, image **b** in inverted gray scale to make the lesions conspicuous and easier to identify them. Continuous yellow arrow indicates the segment IV lesion and the dashed arrow indicates the segment II lesion; the asterisk indicates the spleen. (**c**) Angiography with DEB-TACE attempt where lesions were not clearly circumscribed. The procedure is finalized and CT angiography was performed to characterize lesions, vascularization, and for new therapeutic planning. (**d–f**) Anatomical variant of the celiac trunk with independent emergence of the hepatic artery (green arrow), splenic artery (blue arrow), and left gastric artery (purple arrow), the latter being responsible to irrigate previously documented segment II and IV lesions. Based on this, a new chemoembolization procedure is scheduled (**g–i**), it was performed with selective cannulation of the left gastric artery and embolization was performed with the assistance of the EmboGuide system, which was finally satisfactory. (**g, h**) Yellow arrow indicates the independent origin of left gastric artery; number ***"IV"*** corresponds to lesion of segment IV and the number ***"II"*** is the lesion of hepatic segment ***II***; this same numbering is used in the ***"i"*** image to show the already embolized lesions. (**j–n**) Three months MRI control after DEB-TACE. mRECIST was considered ***stable disease***. Continuous yellow arrow in ***j, q,*** and ***k*** corresponds to embolized lesion of segment ***IV*** in contrast enhanced T1 sequences, diffusion B800 and ADC respectively. The discontinuous yellow arrow in ***l, m,*** and ***n*** corresponds to embolized lesion of segment ***II*** in contrasted T1 sequences, B800 diffusion and ADC respectively, where early enhancement and diffusion restriction of both lesions are evident.

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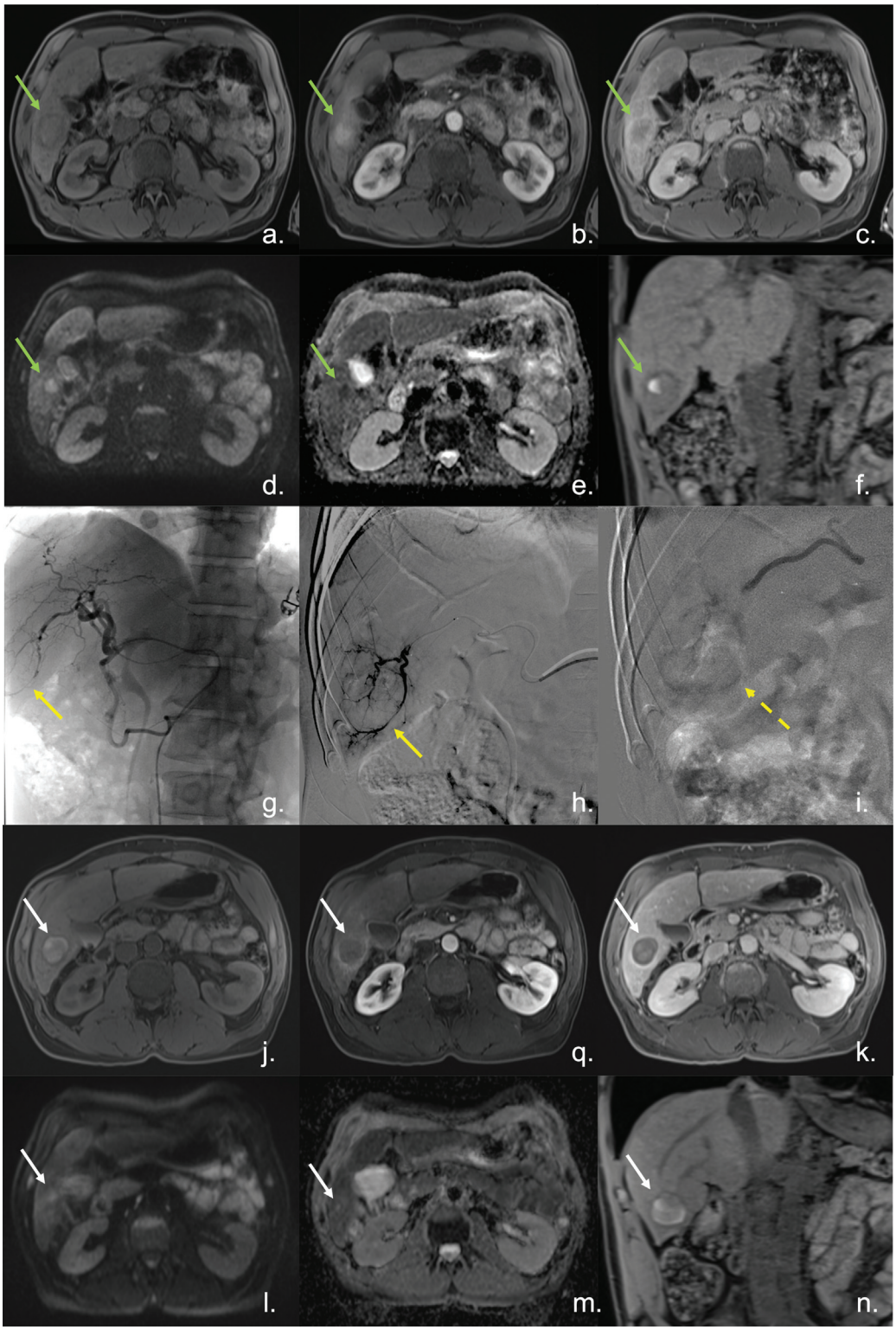

Fig. 5 A 55-year-old, hepatitis C virus cirrhotic patient, multifocal hepatocarcinoma, Child–Pugh A—5 points, ECOG 0, BCLC B, in systemic treatment. MRI with lesion in segment VI [green arrow points out a slightly hypointense lesion with hypointense halo on T1 fat sat **(a)** and small hemorrhagic focus on its interior (**f**) which enhances early after contrast application **(b)**, presents lavage in the portal phase (**c**) and restricts diffusion (***d*** = diffusion B 800 and ***e***: ADC)]. He was treated with DEB-TACE, performing supraselective catheterization of the artery that irrigates the lesion of interest using micro guides (**g, h**), achieving complete embolization with doxorubicin-loaded hepaspheres (**i**: postembolization control). In 3 months of control MRI, reduction in solid component of the lesion is observed, with persistence of a minimal halo of peripheral enhancement and a central hemorrhagic transformation component with minimal restriction to diffusion; ***mRECIST of partial response*** was considered (***j***: axial fat sat T1, **n**: coronal fat sat T1, **q**: early arterial contrast-enhanced T1, **k**: portal contrast-enhanced T1, ***l***: B800 diffusion, **m**: ADC).

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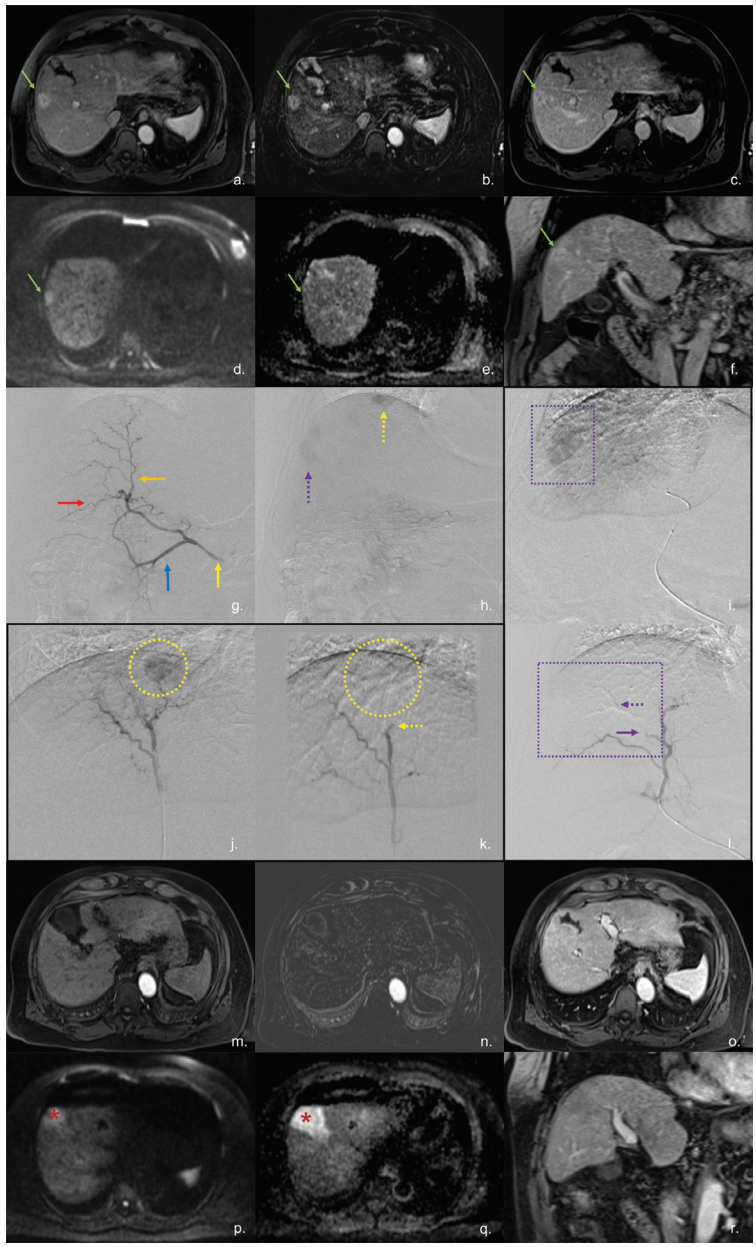

Fig. 6 A 58-year-old patient with cryptogenic cirrhosis and multifocal hepatocarcinoma, Child–Pugh A—5 points, ECOG 0, BCLC B; receive treatment for cirrhosis but not sorafenib. (**a–f**) MRI where HCC is depicted in segment VIII which has early arterial enhancement (**a, b**), central wash out (**c, f**), and restriction to diffusion (**d** and **e**, where **d** is b800 and **e** is the ADC map). (**G–l**) Pictures from arteriography of DEB-TACE therapy. (**g**) Normal arterial irrigation to right hepatic lobe; ***continuous yellow arrow*:** right hepatic artery, ***continuous blue arrow*:** right lateral hepatic artery, ***continuous orange arrow*:** ventral right paramedian artery, ***continuous red arrow*:** dorsal right paramedian artery. (**h**) ***Discontinuous purple arrow*** points out the lesion located in VII segment and ***discontinuous yellow arrow*:** marks out the lesion located subdiaphragmatic in the interline between VII and VIII segments. (***j, k***) Selective arterial microcatheterization of the subdiaphragmatic lesion vascular territory; yellow dotted circle encloses the lesion (**j**) and the place where the lesion is not visualized after embolization (**k**) with its respective stagnant artery pointed out by yellow discontinuous arrow. (**i, l**) Selective arterial microcatheterization of the VIII segment lesion vascular territory; purple dotted square demarcates the lesion (**i**) and the place where lesion is not visualized after embolization (**l**) and its respective stagnant artery pointed out by purple continuous arrow and also the embolization material with purple continuous arrow. (**m–r**) MRI 10 months after DEB-TACE: treated lesions are not visible; so, mRECIST was ***complete response***; red asterisks point out gallbladder. (**a, m:** T1 + gadolinium in early arterial; **b, n:** subtraction. **c, o:** T1 + gadolinium in portal phase. **d, p:** *diffusion–b800*. **e–q**: ADC maps. **f–r:** coronal T1 + gadolinium in portal phase).

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Table 2 Indications and contraindications for intra-arterial therapy in patients with HCC

Reference guide	Inclusion criteria	Contraindications	Evaluation of the therapeutic response
Latin America			
Hospital Universitario Fundación Valle del Lili Cali/ Colombia	1. Patients in intermediate-stage BCLC B: • Extended liver transplant criteria (downstaging intention) • Well-defined nodules + preserved portal flow	**Absolute:** • Decompensated cirrhosis (Child–Pugh > 8 points, jaundice, encephalopathy, refractory ascites, hepatorenal syndrome). • Alterations in portal venous flow (thrombosis, hepatofugal flow). • Tumor involvement of both lobes. • Tumor thrombosis of the portal. • Renal insufficiency (Cr ≥ 2 or creatinine clearance < 30 mL/ min) **Relative:** • Esophageal varices with high risk of bleeding • Tumor size > 10 cm • Severe comorbidities • Incompetent papilla with pneumobilia • Dilation of the bile duct	• LI-RADS treatment response algorithm. • mRECIST
Mexican Guideline[21]	1. Patients with hepatocarcinoma in a context of cirrhosis and with large unresectable tumors, either as a palliative technique or as "bridging" therapy before liver transplantation. 2. Considered if the time on the transplant waiting list exceeds 6 mo 3. Category A of the Child–Pugh 4. A single lesion > 5 cm or multinodular disease (> 3 nodules > 3 cm), without evidence of disease 5. This is a single lesion > 5 cm or multinodular disease 6. (> 3 nodules > 3 cm), without evidence of advanced disease, that is, without portal invasion or disease extrahepatic metastasis 7. ECOG 0, which implies no physical limitation	Unmentioned	Unmentioned
Argentine consensus and guideline[22]	1. Locoregional or "bridging" treatments are recommended in patients with stage T2 HCC in whom the expectation of time on the waiting list is greater than 6 mo 2. Single nodule ≤ 8 cm or 2 or 3 nodules each smaller than 5 cm with a total tumor sum ≤ 8 cm, without macrovascular invasion,	In "downstaging" intention: • More than 3 tumors In palliative intent: 1. Absolute contraindications for TACE are considered 2. The presence of massive tumors with involvement of both lobes 3. Decompensated cirrhosis (Child–Pugh score ≥ 8) 4. Complete absence of portal flow 5. Technical contraindication to intra-arterial treatment	In a downstaging scenario: 1. mRECIST. 2. Milan criteria (re-enter to Milan criteria to evaluate the possibility of transplantation). In palliative setting: 1. mRECIST

(*Continued*)

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Table 2 (*Continued*)

Reference guide	Inclusion criteria	Contraindications	Evaluation of the therapeutic response
Latin America			
	with AFP < 1,000 ng/mL, without extrahepatic manifestations	6. Relative contraindications for TACE are considered: 7. Large tumors (> 10 cm in diameter) 8. Gastroesophageal varices without treatment and with risk of bleeding 9. Portal branch or segmental vein thrombosis 10. Obstruction of the bile duct or incompetent papilla due to surgery or stent	
LAASL[23]	1. Chemoembolization should be considered for patients with BCLC stage B without portal invasion	1. Preoperative transcatheter arterial chemoembolization should not be considered as the standard of care	Unmentioned
Non–Latin American guidelines			
ESMO[34]	1. BCLC A to BCLC B (intermediate), asymptomatic	1. Decompensated cirrhosis 2. High tumor burden 3. Reduced portal vein flow 4. Kidney failure 5. Any technical contraindications to transarterial therapy	RECIST 1.1 or mRECIST Evaluate with magnetic resonance imaging or tomography every 3–4 mo
APASL[33]	1. First-line treatment for unresectable, large/multifocal hepatocarcinoma without vascular invasion or extrahepatic spread 2. It can be performed in patients with small tumors in whom ablation is difficult to perform due to tumor localization or medical comorbidities 3. First-line therapy for downstaging in patients with tumors that exceed the criteria for liver transplantation	Related contraindications: 1. Patients with a significant tumor load (tumor > 50 mm) and Child–Pugh B status 2. STATE score of <18 points	mRECIST
EASL[32]	**Conventional indications:** 1. Patients with BCLC stage B (treated with the selective embolization technique; the TACE and DEB-TACE techniques are considered of similar benefit and either can be used). 2. ECOG performance status of 0–1. **Additional indications to consider:** 1. In early-stage HCC as a bridge-to-transplantation therapy 2. When liver transplantation or liver resection and image-guided ablation are	It should not be used in patients with: 1. Decompensated liver disease 2. Advanced kidney or liver disease 3. Extrahepatic spread or macroscopic vascular invasion 4. An ECOG performance status ≥ 2 5. Inadequate liver function, such as a bilirubin level > 2 mg/dL 6. Tumor load greater than 50% of the total volume of the liver 7. Alteration of portal venous flow (portal venous thrombosis or hepatofugal flow: these are absolute contraindications unless segmental or subsegmental techniques are used in selective therapy)	mRECIST

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Table 2 (*Continued*)

Reference guide	Inclusion criteria	Contraindications	Evaluation of the therapeutic response
Latin America			
	not possible, treatment should be performed with the intention to down-stage and the ability to change the therapeutic strategy	8. Patients with bilioenteric anastomosis or biliary stent due to increased risk of liver abscesses	
AASLD[36]	Patients with hepatocarcinoma presenting cirrhosis in stages T2 (solitary tumor >20 mm with vascular invasion or a multifocal tumor <50 mm) or T3 (multifocal tumor where at least one is >50 mm) without vascular invasion who are not candidates for resection or transplantation and have an adequate physiological condition and liver function classified as Child–Pugh A–B	1. Hepatocarcinoma in advanced stages 2. Child–Pugh C 3. ECOG performance status ≥ 2	mRECIST

Abbreviations: AASLD, American Association for the Study of Liver Diseases; AFP, alfa fetoprotein; APASL, Asian Pacific Association for the Study of the Liver; BCLC, Barcelona Clinic Liver Cancer; DEB-TACE, drug-eluting bead transarterial chemoembolization; EASL, European Association for the Study of the Liver; ECOG, Eastern Cooperative Oncology Group; ESMO, European Society for Medical Oncology; mRECIST, Modified Response Evaluation Criteria In Solid Tumors; RECIST, Response Evaluation Criteria In Solid Tumors; STATE, Selection for TrAnsarterial chemoembolization TrEatment; TACE, transarterial chemoembolization.
Note: Hospital Universitario Fundación Valle del Lili: Reference Hospital in Colombia and Latin America.

enthusiasm to continue improving and refining the technique and indications of this treatment itself.[46]

In the case of Colombia, Prieto-Ortiz et al[47] published a 9-year experience including 152 patients with HCC, showing how TACE can be used in up to 17.3% of patients based on local practice guideline recommendations[21–23]; likewise, median embolization procedures was 1 (IQR 1–2) per patient and mean survival was 15.9 months (6.4–50.2 months); outcome data were consistent in the largest published series of TACE (Holguín et al) and DEB-TACE (Lara-Cárdenas).[5,48]

Scales and Scores to Support Decision-Making

Initial Decision-Making

Decision-making scales and scores regarding to provide TACE is based on the intermediate risk according to BCLC staging system (see ►**Table 1**). Bolondi et al[49] proposed a categorization of 4 levels; and Kudo et al[50] modified it to three-level scale to more accurately predict prognosis and survival of patients trying to provide greater accuracy decision-making tool.

Another scale is *Hepatoma Arterial Embolization Prognostic scale* (HAP).[51] It was created categorizing patients into four stages and each category assumes a probability of *average survival in months*. Patients classified into stages C and D have a poor prognosis and therefore would benefit little from therapies such as TACE compared with patients classified into stages A and B that would receive TACE as their initial therapeutic strategy (see ►**Table 3**). Baca and Ferrer published the experience in a reference center in Lima-Peru validating usefulness of HAP to predict survival at 12 to 24 and 36 months as well as overall mortality in a cohort of 54 patients, documenting that patients with the greatest benefit are category A and B compared with HAP C and D (survival rates at 24 months was 75 and 71.4% and 0% and 0%, respectively).[52]

HAP score has evolved to HAP II by eliminating bilirubins and incorporating portal vein involvement[53] and number of tumor lesions.[54] However, the concordance tests between these modifications and the original scale did not show statistically significant differences.

Other validated scales include *Chiba HCC in intermediate-stage prognostic scale* (CHIP) and *Munich-TACE scale* (see ►**Table 3**). The latter was derived, validated, and compared against the other existing prognostic scales (such as TNM, BCLC, Okuda, and HAP) and showed an area under the curve (AUC) of 0.71 (95% CI: 0.673–0.748) for prediction of *mean survival time*, a value that was higher than other scales evaluated, allowing clinicians to define when to start management with TACE as the first therapeutic measure.[55,56]

Decision-Making for Retreatment with TACE

The first scale considered is the *Assessment for Retreatment with TACE* (ART) score (see ►**Table 3**) which validated three variables as predictive to define the response of 107 patients

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Table 3 Prognostic scales

3.1: HAP scale				
Variable	**Score**	**Stage**	**Points according to the stage**	**Survival (months)**
Albumin < 3.6 g/dL	1 point	HAP A	0 points	32.96
Alpha-fetoprotein > 400 ng/mL	1 point	HAP B	1 point	23.49
Bilirubin > 0.99 mg/dL	1 point	HAP C	2 points	18
Maximum diameter > 7 cm	1 point	HAP D	> 2 points	11.91
3.2: HAP scale				
Variable	**Score**	**Stage**	**Points according to the stage**	**Mean survival (months)**
Albumin < 3.6 g/dL	1 point	HAP A	0 points	129
Alpha-fetoprotein > 400 ng/mL	1 point	HAP B	1 point	42.7
Bilirubin > 0.99 mg/dL	1 point	HAP C	2 points	33.8
Maximum diameter > 7 cm	1 point	HAP D	> 2 points	11.2
Number of tumors ≥ 2	2 points			
3.3: Münich-TACE scale				
Variable	**Score**			
	0	**2**	**3**	**4**	**6**
Alpha-fetoprotein	< 35	–	35–999	–	≥ 1000
Bilirubins	< 1.1	–	1.1-3.0	–	≥ 3.1
C-reactive protein	< 0.5	–	0.5-1.9	–	≥ 2
Creatinine (mg/dL)	< 1.3	≥ 1.3	–	–	–
INR	> 1.2	≤ 1.2	–	–	–
Tumor extension*	**Category A:** (those not classified in Category B)	–	–	**Category B:** 1 nodule > 5 cm Multilocular up to ≤ 3 cm Vascular involvement Metastasis (M1)	–
	Score	**Survival (months)**	**Treatment to consider**		**–**
Low risk	0–9 points	35.2	TACE		–
Intermediate risk	10–13 points	16.9			–
High risk	14–26 points	8.6	Sorafenib as the primary treatment		–
3.4: ART scale					
Variable	**Score**	**Stages**	**Points according to the stage**		**–**
Absence of a radiological response	1 point	Risk group I	0–1.5		–
Increase in AST levels > 25%	4 points	Risk group I	≥ 2.5		–
1-point increase in the Child—Pugh score	1.5 points	–	–		–
≥ 2-point increase in the Child—Pugh score	3 points	–	–		–

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Table 3 (*Continued*)

3.1: HAP scale					
Variable		**Score**	**Stage**	**Points according to the stage**	**Survival (months)**
3.5: STATE scale					
Variable		**Score**		**Points according to the stage**	**Therapeutic group**
Up to 7 (size + number of lesions)	In	0		≥ 18	TACE
	Out	−12		< 18	Alternative therapy
C-reactive protein	< 1 mg/dL	0		–	–
≥ 1 mg/dL	−12	–		–	–
Albumin	g/L	Albumin level		–	–

Abbreviations: ART, assessment for retreatment with TACE; CRP, C-reactive protein; HAP II, hepatoma arterial embolization prognostic version II; HAP, hepatoma arterial embolization prognostic; INR, international normalized ratio; STATE, Selection for TrAnsarterial chemoembolization TrEatment; TACE, transarterial chemoembolization.
Note: STATE score: albumin level (g/L)—12 (if "up to 7" out), 12 (if CRP levels ≥ 1 mg/dL).

to subsequent sessions of TACE applied before 90 days after first session. With this scale, patients are categorized into two groups and survival can be predicted (23.5 vs. 6.6 months; $p < 0.002$).[65]

The Selection for Transarterial Chemoembolization Treatment (STATE) scale (see ►**Table 3**) has also been derived and validated in conjunction with the decision tree using the START protocol (combination of the STATE score and ART strategy), where patients with a poor prognosis can be predicted (STATE < 18 vs. ≥ 18 points, mean overall survival of 5.3 vs. 19.5 months, respectively, $p < 0.001$), being possible to estimate the probability of mortality rate if they would receive the first session of TACE (39 vs. 14%, respectively, $p < 0.001$). The START strategy was also intended to support subsequent therapies of the management based on the previously described results for the ART score and thus define which patients are appropriate candidates for following TACE sessions[56] (see ►**Table 3**), but, in the analysis by Mähringer-Kunz et al, both the score and the strategy had poor performance, which limits their extrapolation and current applicability.[57] Similarly, the α-fetoprotein, BCLC, Child–Pugh and response (ABCR) score did not have sufficient predictive capacity, and neither was superior to the HAP or ART scores for this purpose.[58]

Decision-Making for Retreatment with TACE in Refractory Cases

Although researchers have proposed to use the ART and ABCR scores, those have achieved poor performance in external validation studies, what limits their applicability; therefore, the decision continues to be based on other clinical, laboratory variables and on transdisciplinary decision-making issues, but clinicians are awaiting for better results of algorithms, decision trees, or decision-making tools that could benefit patient outcomes when therapies for refractory cases were offered.[57–59]

TACE

To date, at least 25 clinical trials[61–79] published from 2009 to 2022 have evaluated intra-arterial therapies for HCC (see ►**Table 4**). Among the most striking findings of these studies are that main objectives evaluated are *overall survival*, *time to disease progression*, and *progression-free survival*. Although most studies compare different intra-arterial treatment techniques, a tendency toward a net statistically significant benefit has not been achieved when intra-arterial treatment combined with different types of adjuvant therapy is administered (sorafenib and orantinib, among others). However, in one of the largest studies published to date, Kudo et al (ORIENTAL trial),[79] which compared 445 patients treated with TACE plus orantinib and 444 patients treated with TACE plus placebo, obtained an overall survival of 31.1 and 32.3 months, respectively, and a HR of 1.09 (95% CI: 0.878–1.352; $p = 0.435$). Opposite results were obtained in a meta-analysis performed by Wei et al[80] that evaluated apatinib (also known as rivoceranib, a tyrosine kinase inhibitor that inhibits vascular endothelial growth factor [VEGF] receptor-2) which was suggested to provide a clinical benefit when combined with TACE versus TACE alone in patients with intermediate and/or advanced HCC. Interestingly, when analyzing the results discriminating between non-Asian and Asian populations, the latter patients achieved benefits both in the time to progression (HR: 0.66; 95% CI: 0.48–0.89; $p = 0.006$) and overall survival (HR: 0.57; 95% CI: 0.45–0.72; $p < 0.001$),[81] situation that may indicate over aggregated epigenetic phenomena involved in tumor biology and thus potentially on clinical outcomes.

TACE Plus Neoadjuvant and Adjuvant Therapy

Although TACE therapy in combination with sorafenib has been superior to the use of sorafenib monotherapy in outcomes such as *overall survival* (HR: 0.74, 95% CI: 0.66–0.84; $p < 0.001$), *time to progression* (HR: 0.73, 95% CI: 0.65–0.82;

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Table 4 Controlled trials evaluating the different intra-arterial therapies in hepatocarcinoma from 2009 to 2022

Type of regional therapy	Characteristics of the comparative intervention	Clinical trial/Study name/Author	Year of publication	Intervention and intervention groups	Sample	Main outcome	Results	Reference
TACE	TAE	Okusaka et al	2009	TACE: Zinostatin stimalamer + lipiodol + gelatin sponge particles vs. TAE: Zinostatin stimalamer + lipiodol	TACE: 79 vs. TAE: 82	Survival (2 y)	TACE: 48.2% TAE: 49.6% *p*-value: 0.383	60
		Meyer et al	2013	TACE: Cisplatin 50 mg/50 mL + TAE 4–6 h post-chemotherapeutic infusion vs. TAE: PVA particle 50–150 µm	TACE: 44 vs. TAE: 42	Toxicity RECIST/mRECIST (complete + partial response) median overall survival Progression-free survival	**TAE: TACE: *p*:** Grade toxicity: 63.5%. 83.7% **0.019** RECIST (CR + PR) 13.2% 32.6% **0.04** median overall survival 17.3% 16.3% 0.74 progression-free survival 7.2% 7.5% 0.59	106
		Yu et al	2014	TAE (Trans-arterial ethanol ablation) [Lipiodol plus ethanol 33%] vs. TACE	TAE: 45 vs. TACE: 45	Survival	TAE survival: 24.3 mo 95% CI: 12.8–32.7 TACE survival: 20.1 mo 95% CI: 9.3–31.2 $p = 0.513$	61
	TACE (different chemotherapies)	Ikeda et al (Miriplatin TACE)	2018	TACE (epirubicin + lipiodol) + gelatin particles with pores sized 1–2 mm vs. TACE (miriplatin + lipiodol) + gelatin particles with pores sized 1–2 mm	TACE + epirubicin: 123 vs. TACE + miriplatin: 124	Overall survival	**TACE + epirubicin:** Overall survival time: 1,127 d (95% CI 995–1,300) 2-y survival: 76% (95% CI 68–83) 3-y survival: 53% (95% CI 44–61) **TACE + miriplatin:** Means survival time: 1,111 d (95% CI 888–1,390). 2-y survival: 67% (95% CI 58–75) 3-year survival: 50% (95% CI 41–59) HR 1.01 (95% CI 0.73–1.40) *p*: 0.946	62
	Antityrosine kinase	Park et al (STAH)	2019	TACE + sorafenib vs. Sorafenib	TACE + sorafenib: 170 vs. sorafenib: 169	Survival	**Overall survival:** TACE + sorafenib: 12.8 mo vs. sorafenib: 10.8 mo HR 0.91 95% CI 0.69–1.21 $p = 0.290$ **Secondary goals:** *Mean progression time:* *TACE + sorafenib: 5.3* vs. *sorafenib 3.5 mo* *HR 0.67* *95% CI 0.53–0.85* $p = 0.003$ *Mean progression-free survival:* *TACE + sorafenib: 5.2* vs. *sorafenib: 3.6 mo* *HR 0.73* *95% CI: 0.59–0.91* $p = 0.01$ ***Proportion of tumor response:*** *TACE + sorafenib: 60.6%* vs. *sorafenib: 47.3%* *(p = 0.005)*	81
		Kudo et al (POST TACE)	2011	TACE + sorafenib 200 mg BID Gel foam + lipiodol + chemotherapy (epirubicin, cisplatin,	TACE + sorafenib: 229 vs. TACE + placebo: 227	TTP	TACE + sorafenib: 5.4 mo (95% CI 5% 3.8–7.2 mo) TACE + placebo:	63

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Table 4 (*Continued*)

Type of regional therapy	Characteristics of the comparative intervention	Clinical trial/Study name/Author	Year of publication	Intervention and intervention groups	Sample	Main outcome	Results	Reference
				doxorubicin, or mitomycin) vs. TACE + placebo Gel foam + lipiodol + chemotherapeutic (epirubicin, cisplatin, doxorubicin, or mitomycin)			3.7 mo (95% CI, 3.5–4.0 mo) HR: 0.87 (95% CI 0.70–1.09) $p = 0.252$	
		Kudo et al (TACTICS)	2020	TACE (lipiodol + epirubicin or miriplatin at medical discretion + embolic agent) + sorafenib 400 mg QD × 2–3 wk followed by 800 mg QD vs. TACE (lipiodol + epirubicin or miriplatin at medical discretion + embolic agent) + placebo	TACE + sorafenib: 80 vs. TACE + placebo: 76	Progression-free survival/overall survival	**Progression-free survival:** TACE + sorafenib 25.2 vs. TACE + placebo 13.5 mo; HR = 0.59 95% CI: 0.41–0.87 $p = 0.006$ **Overall survival:** TACE sorafenib: 1 y: 96.2% 2 y: 82.7% TACE + placebo: 1 y: 77.2% 2 y: 64.6%	64
		Kudo et al (ORIENTAL)	2017	TACE (lipiodol + chemotherapeutic + embolic agent) + orantinib 200 mg BID vs. TACE (lipiodol + chemotherapeutic + embolic agent) + placebo	TACE + orantinib: 445 vs. TACE + placebo: 444	Overall survival	**Overall survival:** TACE + orantinib: 31·1 mo (95% CI 26·5–34·5) TACE + placebo: 32·3 mo (28·4–∝) HR 1·090 95% CI 0·878–1·352 *p*: 0·435	79
		Kudo et al (BRISK-TA)	2014	TACE (emulsion of anticancer agent plus lipiodol followed by embolization with embolization agent or injection of microspheres loaded with chemotherapeutic) + Brivanib vs. TACE (emulsion of anticancer agent plus lipiodol followed by embolization with embolization agent or injection of microspheres loaded with chemotherapeutic) + placebo	TACE + Brivanib: 249 vs. TACE + Placebo: 253	Overall survival	TACE + brivanib: 26.4 mo (95% CI: 19.1–infinity) TACE + placebo: 26.1 mo (95% CI: 19–30.9) HR: 0.90 (95% CI: 0.66–1.23)	65
DEB-TACE		Lencioni et al (SPACE trial)	2015	DEB-TACE + sorafenib (300–500 µm microspheres plus doxorubicin) plus sorafenib (400 mg BID) vs. DEB-TACE + placebo (microspheres of 300-500 µm plus doxorubicin) plus placebo	DEB-TACE + sorafenib: 154 vs. DEB-TACE + placebo: 153	Time to progression (TTP)	DEB-TACE + sorafenib: 169 days (95% CI 166–219 d) DEB-TACE + placebo 166 d (95% CI: 113–168 d) HR: 0.797 (95% CI: 0.588–1.080)	66
		Meyer et al (TACE 2)	2017	DEB-TACE (microspheres loaded with doxorubicin sized 100–300 µm then 300–500 µm until slowing the flow) + sorafenib 400 mg BID. vs. DEB-TACE (microspheres loaded with doxorubicin sized 100–300 µm then 300–500 µm until slowing the flow) + placebo	DEB-TACE + sorafenib: 157 vs. DEB-TACE + placebo: 156	Progression-free survival (interval between randomization and progression according to RECIST 1.1 or death from any cause)	DEB-TACE + sorafenib: Progression-free survival: 238 d (95% CI: 221–281). DEB-TACE + placebo: Progression-free survival: 235 d (95% CI: 209–322). HR: 0.99 (95% CI: 0.77–1.27), *p*: 0.94	82
	TAE	Brown et al	2017	DEB-TACE (microspheres loaded with doxorubicin 150 mg + sized 100–300 µm then 300–500 µm then 500–700 µm then PVA 100 µm) vs. TAE (BedBlock sized 100–300 µm then 300–500 µm then 500–700 µm then PVA 100 µm)	DEB-TACE: 50 vs. TAE: 51	RECIST 1.1 2–3 w posttreatment Progression-free survival Overall survival	**Response:** TAE: 5.9% vs. DEB-TACE: 6.0% (difference: −0.1%; 95% CI: −9 to 9%). **Progression-free survival:** ($p = 0.11$; hazard ratio, 1.36; 95% CI, 0.91–2.05) **Overall survival:** ($p = 0.64$; hazard ratio, 1.31; 95% CI, 0.81–2.12)	78

(*Continued*)

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Table 4 (*Continued*)

Type of regional therapy	Characteristics of the comparative intervention	Clinical trial/Study name/Author	Year of publication	Intervention and intervention groups	Sample	Main outcome	Results		Reference
TACE vs. DEB-TACE		Lammer et al (PRECISION V)	2009	DEB-TACE (DC beads with doxorubicin + lipiodol + embolizing particles of the investigator's choice) vs. TACE (doxorubicin + nonionic contrast)	DEB-TACE: 102 vs. TACE: 110		Tumor response	**DEB-TACE** Complete response: 26.9% Partial response: 24.7% Stable disease: 8.3% Disease progression: 40.7%. **TACE** Complete response: 22.2%. Partial response: 21.3%. Stable disease: 8.3%. Disease progression: 40.7%. DEB-TACE vs. TACE: *p*: 0.11	67
		Sacco et al	2011	TACE (lipiodol + doxorubicin + SPONGOSTAN) vs. DEB-TACE (DC bead 100–300 microns + doxorubicin + nonionic iodinated contrast)	TACE: 34 vs. DEB-TACE: 33		Safety, periprocedural toxicity based on liver function and tumor response at 1 mo	**Periprocedural toxicity based on liver function: TACE vs. DEB-TACE:** Higher in TACE ALT: (*p*: 0 .007) Bilirubin: (*p*: 0.003) _____ **Therapeutic response:** TACE Complete response: 70.6% Partial response: 29.4% DEB-TACE: Complete response: 51.5% Partial response: 48.5% (*p*: 0.1)	68
		Puchol et al	2011	TACE (lipiodol + Adriamycin + polyvinyl alcohol) vs. DEB-TACE (Adriamycin + DC Beads 100–300 microns and then 300–500 microns)	TACE: 25 vs. DEB-TACE: 47		Tumor response	**Therapeutic response:** TACE Complete response: 34.7% Objective response: 15.3% Poor response: 19.4% DEB-TACE: Complete response: 65.3% Objective response: 36.1% Poor response: 29.2% (*p*: not significant; there was only a tendency toward better DEB-TACE) :::::::::::::::::::::::::::: **Objective response:** Disappearance or reduction greater than 30% **Poor response:** No response, greater increase of 25% or new lesions	69
		Golfieri et al (PRECISION ITALIA)	2014	DEB-TACE (DC beads of 100–300 μm in diameter loaded with doxorubicin + nonionic contrast medium) vs. TACE (epirubicin + lipiodol + gelatin sponge particles)	DEB-TACE: 89 vs. TACE: 88		Time to progression (TTP)	**TTP:** DEB-TACE: 9 mo (95% CI 6.8–11.2) TACE: 9 mo (95% CI: 6.3–11.7) *p*: 0.766 **Survival:** DEB-TACE 1 y: 86.2% 2 y: 56.8% TACE: 1 y: 83.5%	100

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Table 4 (*Continued*)

Type of regional therapy	Characteristics of the comparative intervention	Clinical trial/Study name/Author	Year of publication	Intervention and intervention groups	Sample	Main outcome	Results		Reference
								2 y: 55.4% *p*: 0.949	
		Facciorusso et al.	2016	TACE (lipiodol + doxorubicin + Gelfoam) vs. DEB-TACE (doxorubicin + DC beads 100–300 microns)	TACE: 104 vs. DEB-TACE: 145		Overall survival	**Overall survival** TACE: 39 mo DEB-TACE: 32 mo HR: 1.33. (95% CI:: 0.94–1.87) $p = 0.1$ **TTP:** TACE: 17 (14–21) mo DEB-TACE: 11 (9–12) mo HR: 2.01 (95% CI: 1.45–2.80) $p < 0.001$	70
Intra-arterial chemotherapy	**Anti-tyrosine kinase**	Kudo et al (SILIUS)	2018	Intra-arterial chemotherapy infusion (cisplatin plus fluorouracil) + sorafenib 400 mg twice daily. vs. sorafenib 400 mg twice daily	QIA + sorafenib: 103 vs. sorafenib: 103	Overall survival	**Overall survival:** HR: 1.009 (95% CI: 0.743–1.371); *p*: 0.955. TTP: HR: 0.645 (95% CI: 0.477–0.872); p: 0.004. Progression-free survival: HR: 0.753 (95% CI: 0.566–1.003); *p*: 0.051		71
	Preclinical phase studies	Ikeda et al. (LEOPARD - Phase II)	2021	Intra-arterial chemotherapy infusion (cisplatin) + lenvatinib	36 patients		Response rate based on RECIST and RECIST 1.1	**Response:** 1. RECIST: 64.7% 2. mRECIST: 45.7% **Survival:** 1. Progression-free: 6.3 mo 2. Overall: 17.2 mo	72
TACE vs. local therapy	**Radiofrequency**	Yang et al	2008	TACE (hydroxycamptothecin + lipiodol + gelatin sponges) vs. RFA. (Insertion of 9-tip 14G WHK-4 multipole trocars needle for 5 cm heat focus guided by CT + radiofrequency dose: 100–150 W 60 times per sec) vs. TACE + RFA vs. TACE + RFA + Lentinan	TACE: 11 RFA: 12 TACE + RFA: 24 TACE + RFA + Lentinan: 31	Survival Tumoral therapeutic response Recurrence rate	**Survival:** *Mean survival*: TACE: 14.9 mo RFA: 18.8 mo TACE + RFA: 21.9 mo TACE + RFA + Lentinan: 28.2 mo *Tumor necrosis*: TACE: 37.5% RFA: 47.8% TACE + RFA: 60.3% TACE + RFA + Lentinan: 88.6% *(the one with greatest benefit; $p < 0.05$)* *Recurrence rate*: TACE: 45.8% RFA: 34.7% TACE + RFA: 29% TACE + RFA + Lentinan: 17.8% *(the one with greatest benefit; $p < 0.05$)*		73
		Shibata et al	2009	RFA. (RFA 1 wk post-TACE with Cool-tip Radiofrequency Ablation System,	RFA: 43 TACE + RFA: 46		Tumor progression Overall survival Local progression	**Tumor progression:** RFA: vs. TACE + RFA:	74

(*Continued*)

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Table 4 (*Continued*)

Type of regional therapy	Characteristics of the comparative intervention	Clinical trial/Study name/Author	Year of publication	Intervention and intervention groups	Sample	Main outcome	Results		Reference
				480-kHz generator; 20–15 cm, 17 G, cold-tipped radiofrequency electrode with 2–3 cm long metal tip; insertion of US or CT guide, 10–12 min of energy, radius of effect 3 cm) TACE + RFA *(TACE: epirubicin + lipiodol + gelatin sponges)*			-free survival Event-free survival	(*p*: 0.797) 1st: 14.4%, 11.4% 2nd: 17.6%, 14.4% 3rd: 17.6%, 14.4% 4th: 17.6%, 14.4% **Overall survival:** RFA: vs. TACE + RFA: (*p*: 0.515) 1st: 100%, 100% 2nd: 100%, 88.8% 3rd: 84.8%, 84.5% 4th: 72.7%, 74.0% **Local progression -free survival:** *p*: 0.934 **Event-free survival:** *p*: 0.365	
		Morimoto et al	2010	TACE (epirubicin + gelatin sponges) vs. TACE + RFA. (RFA on the same day and after TACE with insertion of a 15G needle 15 cm long, focus of ablation of 3.5–4 cm guided by US)	TACE: 18 TACE + RFA: 19		Local tumor production rate Survival rate	**3-y tumor production rate:** TACE: 39% TACE + RFA: 6% (*p*: 0.012) **3-y survival rate:** TACE: 80% TACE + RFA: 93% (*p*: 0.369)	75
		Peng et al	2012	RFA. (15G needles with radius of effect of 3.5 cm + energy 10 W every min until 90 W TACE + RFA (TACE: epirubicin + mitomycin + lipiodol + Gel foam or polyvinyl alcohol to embolize) RFA at 2 wk of TACE	RFA: 70 TACE + RFA: 69		Overall and recurrence -free survival	**Overall survival: (1–3–5 y)** $p = 0.037$ in favor of TACE + RFA **Recurrence -free survival in lesions *3.1–5 cm:* (1–3–5 y)** ($p < 0.002$ in favor of TACE + RFA) **Recurrence -free survival in lesions *smaller than 3 cm:* (1–3–5 y)** p: 0.478 (TACE + RFA vs. RFA)	76
		Peng et al	2013	RFA (15G needles with radius of effect of 3.5 cm + energy 10 W every min until 90 W TACE + RFA (TACE: epirubicin + mitomycin + lipiodol + Gel foam or polyvinyl alcohol to embolize) RFA at 2 wk of TACE	RFA: 95 TACE + RFA: 94		3-y intrahepatic recurrence Overall survival (1–3–4 y) Recurrence -free survival	**3-y intrahepatic recurrence:** RFA: 54.7% vs. TACE + RFA: 35.1% ($p = 0.116$) **Overall survival (1–3–4 y):** HR: 0.525; 95% CI: 0.335–0.822. ($p = 0.002$ in favor of TACE + RFA) **Recurrence-free survival:** HR: 0.575; 95% CI, 0.374–0.897) ($p = 0.009$ in favor of TACE + RFA)	77

Abbreviations: /d, per day; /w, per week; 95% CI, 95% confidence interval; CT, computed tomography; DEB-TACE, drug-eluted bead transarterial chemoembolization; HR, hazard ratio; IAC, intra-arterial chemotherapy; mRECIST, modified Response Evaluation Criteria in Solid Tumors; PVA, polyvinyl alcohol; RECIST, Response Evaluation Criteria in Solid Tumors; RFA, radiofrequency ablation; RFA, radiofrequency ablation; TACE, transarterial chemoembolization; TAE, transarterial embolization; TARE, transarterial radioembolization; TTP, time to progression.

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$p < 0.001$), and *objective response rate* (OR: 2.19, 95% CI: 1.31–3.66, $p = 0.003$),[82] researchers have focused on why therapies combining intra-arterial management (TACE and DEB-TACE) with tyrosine kinase inhibitors have failed to produce significant improvement in outcomes evaluated such as survival or time to progression.[63,66,83,84] Similar results were obtained in studies that tested other inhibitors such as orantinib[80] or drugs with inhibitory effects on endothelial vascular growth factor and fibroblast growth factor such as brivanib.[65] However, in the TACTICS study,[64] there was an improvement in *progression-free survival* of patients treated with TACE therapy plus sorafenib from 13.5 to 25.2 months for a HR of 0.59, $p = 0.006$, and the 1- and 2-year survival rates were higher in the group of patients treated with the intervention plus sorafenib.[64] Notably, the TACTICS study is one of the studies that included the smallest number of patients and it is the only study reporting different results but used a protocol of administering sorafenib with doses higher than those conventionally used.

Another intra-arterial treatment modality is transarterial infusion chemotherapy (TAIC) without embolization. This treatment has been evaluated and compared with the use of sorafenib versus placebo.[71] A benefit for outcomes such as *survival* was not identified (HR: 1.009, 95% CI: 0.743–1.371), although among the secondary objectives, a tendency toward a benefit in the *time to progression* was observed when intra-arterial chemotherapy was provided in combination with sorafenib ($p = 0.004$), but *progression-free survival* did not achieve a significant difference between groups ($p = 0.051$).

When the origin of HCC is hepatitis B, there is possibility of virus and subsequent reactivation of hepatitis after TACE; thus, preventive antiviral therapy has been considered. This therapy is considered neoadjuvant and adjuvant among systemic therapies within this context. According to the meta-analysis by Zhang et al,[83,85] the risk for viral reactivation was an OR of 3.70 (95% CI: 1.45–9.42; $p < 0.01$), and the risk of hepatitis was an OR of 4.30 (95% CI: 2.28–8.13; $p < 0.01$). Preventive antiviral therapy was beneficial for reducing viral reactivation (OR: 0.08; 95% CI: 0.02–0.32; $p < 0.01$) and hepatitis (OR: 0.22; 95% CI: 0.06–0.80; $p = 0.02$).

TACE versus TACE Plus Another Local Therapy

Most of published studies comparing nonvascular local therapies have been evaluated. Several meta-analyses reveal benefits of combined therapy TACE plus local therapies without evidence of increase in complications rate related to local therapies.[122–131]

Two clinical trials examined TACE plus microwave or radiofrequency ablation. The first was performed by Sheta et al[87] including 50 patients with Child—Pugh A–B disease and tumor lesion >4 cm confined to one hepatic lobe. Twenty patients were randomized to receive TACE, 20 to receive thermal radioablation, and 10 to receive microwave ablation. Success rate at 6 months was 50% for TACE group, 70% for the TACE plus thermal radioablation group, and 80% for the TACE plus microwave ablation group, with no significant difference in recurrence at 6 months ($p = 0.923$). However, greater recurrence was observed at 1 month in TACE group compared with the group receiving TACE therapy plus local therapy interventions ($p = 0.027$). Zaitoun et al[132] conducted one of the largest studies to date in patients with HCC size >3 cm and <5 cm. They recruited 90 patients for TACE, 95 patients for microwave ablation, and 93 patients for TACE plus microwave ablation. Results showed that mRECIST at 1 month ($p = 0.0002$), recurrence at 12 months ($p = 0.0001$), *overall mortality rate* ($p = 0.02$), *overall survival* ($p = 0.02$), *mean survival time* in months ($p = 0.02$) and *progression-free survival* ($p < 0.001$) were statistically better and combined therapy was significantly favored (TACE plus microwave ablation) over each therapy alone.

Two studies published by Peng et al with similar inclusion criteria that compared TACE plus radiofrequency ablation versus radiofrequency ablation alone described how the combined intervention is more useful in terms of improved outcomes such as *survival* and *recurrence-free survival* as a function of the tumor size. They showed no benefit in patients with lesions <3 cm, but TACE plus radiofrequency ablation was superior to radiofrequency ablation alone in improving survival for patients with tumors measuring less than 7 cm.[76,77] The benefits in patients with lesions measuring 3 to 5 cm (up to a total of three lesions) have also been previously published by Morimoto et al in 2010,[75] and the absence of benefit for patients with lesions <3 cm was documented by Shibata et al.[74] The scenario in which radiofrequency ablation has greater therapeutic efficacy is clear, but Wang et al[88] suggested an additional improvement in quality of life by adding to treatment *lentinan* (polysaccharide isolated from Shitake fungi, which has anticancer properties).[73] Thus, this therapeutic strategy represents an additional option and alternative in the therapeutic arsenal for HCC.

DEB-TACE

DEB-TACE has evolved from TAE to manage HCC and tried to reduce the incidence of adverse effects and improve the therapeutic outcomes of TACE (see ►**Table 5** for characteristics of the most used microspheres and ►**Figs. 4–6**). This technique consists fundamentally in use of ionically charged microspheres capable of actively sequestering cytotoxic drugs that will subsequently be slowly released within the target lesion, allowing strict control of the dose administered locally in tumoral lesion and favoring exposure to antineoplastic drugs and reducing systemic toxicity.[89]

In the published observational analytical research, DEB-TACE is as good as TACE without clear differences in *survival* or *therapeutic efficacy*, and these good results are presumed to be mainly due to lower liver toxicity, better tolerance, and a shorter hospital stay.[90–92] The potential benefit in terms of cost-effectiveness is based on improvement in quality-adjusted life years (QALY; DEB-TACE 4 vs. TACE 3.3 QALY), despite the increase in direct costs incurred by DEB-TACE therapy according to the meta-analysis of Cucchetti et al.[93]

Relevant item for this therapy is its usefulness in *downstaging*, allowing the return of resectable lesions or lesions that can be managed with locoregional therapies such as

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Table 5 Most common types of beads available for DEB-TACE treatment

Bead brand	Derived product	Biochemical characteristics	Presentation	Drugs it carries
DC Bead *(Boston Scientific—United States)*	Polyvinyl alcohol modified with sulfonate groups to form a hydrogen bond with the drug; it displays high-water content (95%)	1. Biocompatible 2. Hydrophilic 3. Nonresorbable 4. Ion exchange loading mechanism (active process) with sequestration as efficient as 99% and a maximum load of 45 mg/mL (range 5–45 mg/mL) for hydrated beads	1. 100–300 μm 2. 300–500 μm 3. 500–700 μm	1. Doxorubicin 2. Irinotecan 3. Epirubicin
DC Bead LUMI *(Boston Scientific—United States)*	Polyvinyl alcohol type	1. Biocompatible 2. Radiopaque 3. Nonresorbable hydrogel	1. 40–90 μm. 2. 70–150 μm. 2. 100–300 μm. 3. 300–500 μm	1. Doxorubicin 2. Irinotecan
HepaSphere *(Merit Medical—United States)*	Monomers of vinyl acetate and methyl acrylate that form a copolymer (sodium alcohol acrylate)	1. Biocompatible 2. Nonresorbable 3. Expandable 4. Each wire	1. 30–60 μm 2. 50–100 μm 3. 100–150 μm 4. 150–-200 μm	1. Doxorubicin 2. Irinotecan 3. Epirubicin 4. Oxaliplatin
TANDEM *(Varian Medical—United States)*	Polymethacrylate hydrogel that contains two parts, the center, which is the molecule described above, and an inorganic coating of Polyzene-F (perfluorinated polymer)	1. The chemotherapeutic drug can be loaded on beads up to 50 mg/mL 2. They have a negative charge	1. 30–50 μm 2. 60–90 μm 3. 75–125 μm	1. Doxorubicin 2. Idarubicin 3. Epirubicin 4. Irinotecan

ablative therapies. Similar situation has been observed in patients who had been excluded from the transplant option, where after treatment with DEB-TACE they can be considered again as candidates.[94] In addition, the favorable outcomes also seem to be associated with the size of the microspheres, as smaller microspheres seem to produce better outcomes.[95,96]

A feared complication of microspheres is the systemic embolism of patients who have arteriovenous shunts at the portosystemic level, which has also been associated with the use of larger microspheres.[97] Thus, interventions have been proposed with selective occlusion of hepatic veins with temporary occlusion balloon catheter through the transfemoral or transjugular route at the time of arterial injection to subsequently isolate the shunt and prevent systemic embolism. This intervention has been evaluated by Lee et al in 11 patients and achieved 100% technical success without evidence of pulmonary complications.[98]

Some of the most important preclinical studies in DEB-TACE was conducted by Varela et al and published in 2007, where they evaluated the safety, pharmacokinetics, and efficacy in cirrhotic Child—Pugh A patients with large or untreated multifocal HCC. They provided chemoembolization with microspheres loaded with doxorubicin. Response rate was 75% with a 1-year survival rate of 92.5% and a 2-year survival rate of 88.9%.[108] Subsequently, series of studies evaluating the usefulness of DEB-TACE combined with sorafenib were published[66,91] along with comparisons between TACE versus DEB-TACE.[67,69,70,100] These studies reported results like those previously obtained by analytical observational cohorts (see ►**Table 4**) and were reinforced by the results of meta-analysis where the *complete response, partial response, disease control rate, stable disease, the global responses at 3, 6, 9 and 12 months,* and *overall survival and complications* were not different between patients treated with TACE and DEB-TACE.[101]

Bland Embolization

Compared with TACE and DEB-TACE, TAE uses microspheres without chemotherapeutics. The evolution of technique has made it possible to have options of different molecules using microparticles with diverse features and different results,[102,103] probably allowing to reduce retreatments with TACE that is usually required in these patients; however, multiple sessions of TAE may be required in the same vessel, as documented by Erinjeri et al, who demonstrated that 83% of patients did not change the vascular anatomy in up to five arteriographic controls made of TAE therapy despite circulatory blockage in each therapy.[104]

There are data demonstrating on-superiority of TACE or DEB-TACE versus TAE and others demonstrate the benefits of each therapeutic modality. A pioneering study exploring TAE is the study by Kawai et al[105] who studied 289 patients and evaluated TACE with lipiodol plus Adriamycin versus TAE only with lipiodol, in both cases occluding the nutrient artery with gelatin sponges. The size reduction >50% in the imaging control at 4 weeks was 26.8 versus 27.5%, respectively

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(p = NS), and 3-year survival did not differ ($p = 0.209$). Meyer et al also performed a phase II clinical trial with 86 patients with a different and innovative scheme of TACE plus cisplatin. They performed embolization with 50 to 150 µm PVA microparticles and compared it with TAE. Nonsignificant survival was obtained (RR = 95% CI: 0.62–1.47), and no other outcome was favorable.[106] Two studies analyzed by propensity match score but with different sample sizes (Massarweh et al[107] with 405 patients and Roth et al[108] with 205 patient), showed no difference in clinical outcome, but radiological response was significant in favor of TACE.

Malagari et al conducted a randomized controlled trial of DEB-TACE (Doxorubicin) versus TAE (BeadBlock) in 84 patients and demonstrates superiority in recurrence at 12 months ($p < 0.0001$) with a trend toward superiority from 3 months in favor of DEB-TACE, with a greater complete response at 6 months (26.8 vs. 14%) as well as a longer time to progression with DEB-TACE versus TAE (42.4 vs. 36.2 wk, respectively; $p = 0.008$).[109]

Some data have been in favor of TAE and have shown usefulness in survival ($p = 0.03$) for the management of recurrences in single lesion in patients who have been managed with partial hepatectomy[110] having greater positive impact in overall survival at 1 to 3 and 5 years in single lesions up to 7 cm when combined with ablative therapy (radiofrequency or ethanol)[111,113] and in intermittent combined therapies between TAE (attempt to partially reduce tumor load) and TACE for large lesions with good results in terms of survival.[112]

Perhaps one of the most important studies of TAE is Brown's article, in which a single tertiary reference center study was randomized 101 patients to TAE with microspheres (BeadBlock 100–300 µm) versus DEB-TACE with doxorubicin (100–300 µm). In this study, TAE with microspheres did not show statistically significant differences with DEB-TACE with doxorubicin in progression-free survival ($p = 0.11$; HR: 1.36; 95% CI: 0.91–2.05) or overall survival ($p = 0.64$; HR: 1.31; 95% CI: 0.81–2.12).

It is important to emphasize that of the total cohort, the predominant stage was Okuda I (81.1%), 21.7% of patients were early-stage BCLC (A), and only 44.5% corresponded to intermediate-stage BCLC (B), a situation to be considered when comparing it with results of other intra-arterial therapies, since it included a considerable number of population different from intermediate stage, reflecting results of meta-analysis where no superiority of any intra-arterial intervention over another in the conclusion, but the heterogeneity observed makes interpretation of these results difficult.[104]

However, it is quite interesting how a network meta-analysis with different analysis models shows benefit for all therapies with probable nonsuperiority of one over the other, but increased benefit as locoregional therapies is added to regional vascular therapies (adding therapies such as radiotherapy or ablative therapies to intra-arterial therapies), this being a striking proposal and commitment for future decisions in transdisciplinary meetings at the time of defining treatments for patients.[114]

Immunotherapy and Combination with Locoregional Treatments

Immunotherapy is a promising intervention in the treatment of HCC and has extensive and interesting physiological, pathophysiological, and pharmacological substrates to which we refer the readers to other reviews.[115] However, ablative therapies or therapies that induce ischemia/infarction determine the release of tumor-associated antigens that generate an increase in the immune response directed at the neoplastic lesion itself, but HCC has multiple immunological phenomena that result in a deviation of the expected immune response to neoplastic cells.

Many of these changes lead to aberrant responses of different lymphocyte lineages, a decrease in proinflammatory cytokines (tumor necrosis factor [TNF]-α, interferon [IFN]-gamma, and interleukin [IL]-1) and an increase in the production of immunosuppressive cytokines (IL-4, IL-5, IL-8, and IL-10), all resulting in an inefficient antitumor response that may explain relapse even in patients who have received a liver transplant.[117]

Locoregional therapies are powerful treatments to stimulate the presentation of neoantigens from tumor cells to antigen-presenting cells (mainly dendritic cells) and subsequent activation of the expected inflammatory response to achieve the desired antitumor effects.[119] For example, TACE decreases the numbers of *Treg* (regulatory T cells) and *CD8+ T cells* but increases glypican 3 (GPC3)-expressing cytotoxic T lymphocytes (CTLs), IL-6 production, CD4+ T cells, and the CD4 +/CD8+ natural killer (NK) cell ratio, which promote the activation of the immune response against the tumor lesion.[120]

On the other hand, *immune checkpoint inhibitors* are a series of regulatory molecules expressed by immune cells that regulate the degree of immune activation and usually act as inhibitors, playing an important role in preventing autoimmune disease through biological self-tolerance.[122] HCC cells express proteins that activate *immune checkpoints* (e.g., programmed cell death receptors and their ligands, such as PD-1 and PD-L1/PD-L2, and proteins associated with cytotoxic T lymphocytes, such as cytotoxic T lymphocyte-associated antigen-4 [CTLA-4]). Therefore, the previously described tumor antigens are not presented to T cells, and the response necessary for tumor control is not activated.

Based on this information, specific antibodies have been created (anti-PD-1, anti-PD-L1, anti-CTLA-4, anti-VEGF, etc.) that fundamentally activate the functions of weakened or blocked cells as "*immune checkpoint inhibitors*" (e.g., *nivolumab, pembrolizumab, atezolizumab, and camrelizumab*). Currently, these drugs are undergoing evaluation in Phase III clinical trials, and we anticipate obtaining promising results. This optimism is based on the promising immunogenic effects observed in intra-arterial therapies promoted by ischemia/infarction, along with immunological modulation within the pathways that sustain immunosuppression via immune checkpoint inhibitor mechanisms. (see ►**Table 6**).

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Table 6 Phase III trials under development that are evaluating TACE and immunological therapy

Name of the clinical trial	Abbreviated name	Clinical trial identifier	Inclusion criteria	Estimated end	Interventions	Evaluated outcomes
Study of adoptive transfer of iNKT cells combined with TACE to treat advanced HCC	Not provided	NCT04011033	• Age: 18–80 y • Patients with BCLC Stage C HCC diagnosed by histology or by imaging with relapse after previous therapy AND without effective therapy known at the time • Life expectancy $\geq$ 12 wk • Absence of hematological or renal involvement, iNKT cells > 10/mL among peripheral blood mononuclear cells	2021 (unpublished data, study status unknown)	TACE + iNKT cells + cyclophosphamide + recombinant human IL-2. vs. TACE	Overall survival Progression-free survival Disease control rate
DEB-TACE plus lenvatinib or sorafenib or PD-1 inhibitor for unresectable hepatocellular carcinoma	Not provided	NCT04229355	• Age: 18–75 y • Patients with unresectable primary hepatocarcinoma • Child–Pugh A liver function	2022	DEB-TACE + sorafenib vs. DEB-TACE + lenvatinib vs. DEB-TACE + PD-1 inhibitor	Progression-free survival
A Global Study to Evaluate Transarterial Chemoembolization (TACE) in combination with durvalumab and bevacizumab therapy in patients with locoregional hepatocellular carcinoma	EMERALD-1	NCT03778957	• No evidence of extrahepatic disease • Disease not suitable for curative surgery or transplantation or curative ablation but suitable for TACE • Child–Pugh A to B status • ECOG performance status of 0 or 1 • Measurable disease according to mRECIST criteria • Proper function of organs and marrow	2024	Tremelimumab + durvalumab + TACE + lenvatinib vs. tremelimumab + durvalumab + TACE vs. TACE	Progression-free survival according to the RECIST1.1 criteria
A Study of Nivolumab and Ipilimumab and Nivolumab Alone in Combination with Trans-arterial ChemoEmbolization (TACE) in Participants with Intermediate Stage Liver Cancer (CheckMate 74W)	CheckMate 74W	NCT04340193	• Patients with intermediate-stage HCC whose tumor characteristics exceed the Milan and Up-to-7 (BMU7) criteria and are eligible for TACE • The tumor does not exhibit extrahepatic spread, regional lymph node involvement, main portal vein thrombosis, main left or main right portal vein thrombosis, or macrovascular invasion. • ECOG performance status of 0 or 1	2024	Nivolumab + Ipilimumab + TACE vs. Nivolumab + TACE vs. TACE alone	Time to progression until TACE is not possible Overall survival
TACE Combined with Penpulimab and Anlotinib for Advanced HCC	Not provided	NCT05344924	• Clinical pathological diagnosis of carcinoma • Age: 18–80 y • BCLC Stage C. • Life expectancy greater than 12 wk	2024	TACE + Penpulimab + Anlotinib vs. Penpulimab + Anlotinib	Progression-free survival
The ABC-HCC Trial: Atezolizumab Plus Bevacizumab vs. Transarterial Chemoembolization (TACE) in Intermediate-stage HCC	ABC-HCC Trial	NCT04803994	• Patients aged $\geq$ 18 y • Diagnosis of HCC based on histopathology or typical diagnostic imaging according to AASLD criteria • Disease not suitable for curative surgery or	2025	Atezolizumab + Bevacizumab vs. TACE	Time to treatment failure

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Table 6 (*Continued*)

Name of the clinical trial	Abbreviated name	Clinical trial identifier	Inclusion criteria	Estimated end	Interventions	Evaluated outcomes
			transplantation or curative ablation but suitable TACE. • The extent of the disease is classified according to the following parameters: - Multifocal HCC beyond the Milan criteria (i.e., >3 lesions of any size or ≥ 2 lesions with at least one ≥ 3 cm) - More than one untreated nodule of HCC >10 mm showing arterial hyperenhancement without a massive multinodular pattern preventing adequate TACE - No diffuse infiltrating HCC tumor - Permeable portal vein flow - No invasion/thrombosis of the portal vein (including segmental) on baseline/eligibility images - No extrahepatic disease - Child–Pugh A status without ascites requiring more than 100 mg spironolactone/day - ECOG performance status of 0 - Proper organ and bone marrow function - Life expectancy of ≥ 3 mo			
A Study of TACE Combined with Camrelizumab Plus Rivoceranib (Apatinib) in Patients with Incurable Hepatocellular Carcinoma	Not provided	NCT05320692	• HCC diagnosed by histopathology/cytology • At least one measurable lesion • Child–Pugh A status • ECOG performance status of 0 or 1	2026	TACE + Camrelizumab + Apatinib mesylate vs. TACE	Progression-free survival
Nivolumab in Combination with TACE/TAE for Patients with Intermediate Stage HCC	TACE-3	NCT04268888	• Histological diagnosis of HCC and at least one measurable lesion according to the RECIST 1.1 criteria • Not a candidate for surgical resection or liver transplantation Age ≥ 16 y and estimated life expectancy >3 mo ECOG performance status of 0–1 • Adequate hematological function Bilirubin level ≤ 2.9 µmol/L, AST, ALT, and ALP levels $\leq 5 \times$ LSN • Adequate kidney function INR ≤ 1.6 • Child–Pugh A	2026	Nivolumab + TACE/TAE vs. TACE/TAE alone	Time to progression until TACE can be performed Overall survival

(*Continued*)

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Table 6 (*Continued*)

Name of the clinical trial	Abbreviated name	Clinical trial identifier	Inclusion criteria	Estimated end	Interventions	Evaluated outcomes
			• HAP A, B, or C score • No contraindications to therapy with T cell "check point control" inhibitors Not pregnant			
A Study of TACE Combined with Atezolizumab Plus Bevacizumab or TACE Alone in Patients with Untreated Hepatocellular Carcinoma	TALENTACE	NCT04712643	• Confirmed diagnosis of HCC based on histology/cytology or clinical criteria • Eligible for TACE treatment • No prior systemic treatment for HCC, especially immunotherapy • No locoregional therapy prior to the treatment of the target lesion(s) • At least 1 measurable untreated lesion • ECOG performance status of 0–1 • Child–Pugh A status	2027	Atezolizumab + bevacizumab + TACE vs. TACE	TACE: Progression-free survival Overall survival
Evaluate durvalumab and tremelimumab +/− lenvatinib in combination with TACE in patients with locoregional HCC	EMERALD-3	NCT05301842	• No evidence of extrahepatic disease • Disease not suitable for curative surgery or transplantation or curative ablation but suitable for TACE • Child–Pugh A to B status • ECOG performance status of 0 or 1 • Measurable disease according to mRECIST criteria • Proper function of organs and marrow	2027	Durvalumab + TACE vs. Durvalumab + Bevacizumab + TACE vs. TACE alone	Comparison of progression-free survival according to the RECIST 1.1 criteria between intervention arms A and C
Safety and Efficacy of Lenvatinib (E7080/MK-7902) with Pembrolizumab (MK-3475) in Combination with Transarterial Chemoembolization (TACE) in Participants with Incurable/Non-metastatic Hepatocellular Carcinoma (MK-7902-012/E7080-G000-318/LEAP-012)	LEAP-012	NCT04246177	• HCC confirmed by radiology, histology, or cytology. • HCC located in the liver and is not amenable to curative treatment • Participants infected with HCV are eligible if treatment was completed at least 1 mo before starting the study intervention • Participants infected with HBV are eligible • Blood pressure is controlled with or without antihypertensive medications • Proper function of the organ	2029	Lenvatinib + pembrolizumab + TACE vs. TACE alone	Progression-free survival according to RECIST 1.1 criteria Overall survival

Abbreviations: AASLD, American Association for the Study of Liver Diseases; ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate aminotransferase; BCLC, Barcelona Clinic Liver Cancer; BMU7, Category B, Milan "up to 7 criterion"; DEB-TACE, drug-eluting bead transarterial chemoembolization; ECOG, Eastern Cooperative Oncology Group; HAP, hepatoma arterial embolization prognostic; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; iNKT cells, invariant natural killer T cells; LSN, low score normal; mRECIST, modified Response Evaluation Criteria In Solid Tumors; PD-1, programmed cell death protein 1; RECIST, Response Evaluation Criteria In Solid Tumors; TACE, transarterial chemoembolization; TAE, transarterial embolization.

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Complications

TACE has been considered a safe therapy with a low incidence of complications; however, it is not exempt from them. Fortunately, most of these events are National Cancer Institute **C**ommon **T**erminology **C**riteria for **A**dverse **E**vents (CTCAE) grades 1 and 2 (71.7 and 11.2%, respectively). The incidence of major complications ranges from 0.3% to 1.8% and includes conditions such as edematous-ascitic decompensation, acute cholecystitis, acute pancreatitis, liver abscess, hepatic rupture, and acute renal dysfunction. Minor complications occur at rates of approximately 5% to 22%, with the most frequent being the post-embolization syndrome, which has an incidence of 22%, although some other authors report it as high as 60% to 80%. This syndrome consists of abdominal pain, nausea, fever, and elevated transaminase levels between 24 and 72 hours after the procedure), followed by abdominal pain (20%) and fever (19%).[122] Other authors also evaluated the systemic inflammatory response syndrome within the complications, and it has been reported in up to 61.5% of patients, indicating that it is among the most frequent adverse events.[123]

Although renal failure is among the minor complications and indeed has a low incidence, Mou et al published a meta-analysis describing the effect of this condition on patients undergoing TACE and observed that risk of death is 3.74 times higher in patients who develop acute renal dysfunction than in patients who do not present this complication.[125]

An event of frequent concern is the possibility of hepatic arterial complications in the postoperative period of liver transplantation in patients who have previously received TACE. However, Sneiders et al reported that up to 6.6% of patients present this type of complication and OR compared with transplanted patients without TACE was 1.73 (95% CI: 0.82–3.63; $p = 0.149$), thus refuting the possibility of TACE and higher incidence of arterial complications in the liver transplant period.[125]

In general, DEB-TACE has a lower incidence of side effects than TACE; however, the data are contradictory in published results.[127] A different situation occurs when TACE is compared with therapies such as radiofrequency, where no substantial differences in the incidence of complications are observed.[127]

Finally, complications that occur at a very low frequency but have been documented in case series or case reports include necrosis of the bile duct, pseudoaneurysms in the hepatic arterial circulation, and ischemic gastroduodenal ulcers, which are probably related to vascular complications due to vascular manipulation during intra-arterial therapy itself.[128–130]

Conclusions

The incidence and prevalence of HCC are increasing. A probable explanation is the epidemiological transition that is observed, where the increase in chronic liver disease related to NASH might explain it, but in some Latin American countries viral disease continues to be of big importance. Currently, a diagnosis based on images is available, where the presence of HCC can be defined with high precision according to its behavior in dynamic studies based on the kinetics of the contrast medium. This diagnosis may be complemented with evaluations of the liver function, overall clinical conditions and staging with different scales/scores available for this purpose, and is the most frequently used BCLC system, accepted and adopted in current practice and in different therapeutic flowcharts.

In patients with intermediate-stage tumors, different therapeutic options have been proposed including locoregional treatment options with intra-arterial therapies that initially was developed as a palliative intervention; however, with the extended indications currently available, therapeutic options in the modalities of "*bridge-to-transplantation therapy*," "*downstaging therapy*," and finally *palliative therapy* can be provided to produce positive effect on some outcomes such as *survival and progression-free survival*, among others. Intra-arterial therapies can be repeated at regular intervals or depending on tumor response but should be discontinued in case of untreatable progression (this situation is defined as progression associated with a profile that determines a contraindication for the procedure, such as decompensation of liver disease, vascular invasion, or extrahepatic spread) or when significant impact on hepatic functional reserve is reducing the opportunity for patients accessing to different therapeutic steps; this is a part of transdisciplinary medical judgment when to stop this therapeutic option.

Researchers have attempted to optimize therapeutic decision-making with different scales/scores derived and validated for this purpose; however, among all of them the Munich-TACE scale probably exhibits the highest performance to define who should receive the intra-arterial therapies compared with pharmacological management as an initial measure. However, for other scenarios, such as retreatment or retreatment after therapeutic failure, these scales have not had sufficient statistical power to be superior to the clinical and multidisciplinary approach.

The association of TACE with many molecular agents (such as sorafenib or brivanib and so on) has not conclusively demonstrated an improvement in response rate, time to tumor progression, or survival; so, its use is not fully recommended.

From the technical perspective, substantial differences in the outcomes of TAE, TACE, and DEB-TACE have not been observed; however, we hope that with better quality of available evidence, we could define with better precision what type of therapy is better for each case to achieve best possible results. Importantly, a greater efficiency of DEB-TACE has been documented in terms of the increase in QALY adjusted for the costs that increases with this therapy and it is achieved by theoretical lower incidence of systemic adverse events based on the way this therapeutic modality delivers the chemotherapeutic and TAE could be topic of discussion for some cases.

The combination of multiple therapeutic modalities, including local, regional, and systemic therapies, is developing

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and evolving. Within the latter category, immunological therapies have all the biologically plausible effects to ensure greater efficiency in generating the desired outcomes (at least of local tumor control). We are awaiting multiple phase III studies that will help us obtain more data for the implementation of these therapeutic combinations and positively affect the multimodal and transdisciplinary management that the patient with HCC deserves.

Finally, management of these patients in Latin America continues to be a challenge; however, great efforts have been made to achieve clinical practice guidelines and consensus that facilitate decision-making, thus allowing results that do not seem to be very dissimilar with those reported in other regions. Therefore, it is important to emphasize that there are social and accessibility barriers as variables that could have significant impact on patients' outcome in our region, even when quality interventions are being brought to our populations and it is necessary to continue with efforts to join strengths that allow us to know on larger scale the impact of interventions such as those performed from the interventional field in patients with HCC to have information that guarantee qualified decision-making therapies in our regions and that it could impact positively patients with HCC, which is becoming more prevalent and has a great effect at public health level.

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