Chapter 3
HCC

Franco Orsi

3.1 Introduction

Hepatocellular carcinoma (HCC) ranks among the most common cancers worldwide, representing the sixth most common one, the third cause of cancer-related death, and accounts for 7% of all cancers [1]. HCC represents more than 90% of primary liver cancers and is a major global health problem. Over the last three decades, the age-adjusted incidence of liver cancer has risen to 4.6 per 100,000 individuals. The incidence of HCC will likely continue to rise as the hepatitis C epidemic reaches maturity and nonalcoholic steatohepatitis becomes more prevalent. The incidence of HCC increases progressively with advancing age in all populations, reaching a peak at 70 years [2].

Approximately 90% of HCCs are associated with a known underlying risk factor: the most frequent factors include chronic

F. Orsi
Interventional Radiology Division, European Institute of Oncology, Milan, Italy
e-mail: franco.orsi@ieo.it

© Springer International Publishing AG 2018

E. Van Cutsem et al. (eds.), *Locoregional Tumor Therapy*,
https://doi.org/10.1007/978-3-319-69947-9_3

viral hepatitis (types B and C), alcohol intake, and aflatoxin exposure. In the developed Western world, only 20% of cases can be attributed to HBV infection, while chronic hepatitis C appears to be the major risk factor [3].

Cirrhosis is the other most important risk factor for HCC and may be caused by chronic viral hepatitis, alcohol, and other inherited metabolic diseases. All etiologic forms of cirrhosis may be complicated by tumor formation, but the risk is higher in patients with hepatitis infection. Overall, one-third of cirrhotic patients will develop HCC during their lifetime [4].

Recent studies have shown that liver cancer incidence increases in parallel to portal pressure as directly measured [5] or in parallel to the degree of liver stiffness as measured by elastography [6, 7].

The presence of cirrhosis influences the chance for anticancer treatment, affecting their results. Then, many available treatments can have an adverse impact on cirrhosis and the exact cause of death, which could be either the underlying disease or HCC.

3.2 Diagnosis

Early stage of HCC may be treated with potentially curative procedures such as resection, percutaneous ablation, and transplantation. Thus, there is an urgent need to identify better tools for detecting and characterizing these lesions in order to improve clinical outcome of HCC patients. Diagnosis of small HCC is feasible in 30–60% of cases, and this enables the application of curative treatments.

Until 2000, diagnosis was based on biopsy, and then a panel of experts reported, for the first time, noninvasive criteria (see Fig. 3.1) for HCC, based on a combination of imaging and laboratory findings [8]. The dynamic radiological contrast enhance-

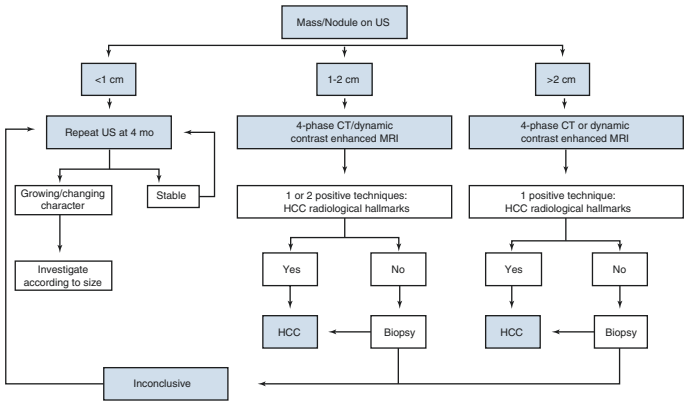

Fig. 3.1 Diagnostic algorithm for HCC in cirrhotic patients [8]

ment in the arterial phase by CT, MRI, angiography, or US (CEUS) represents the most important finding for the radiological diagnosis of early HCC.

The clinical evaluation and management of HCC require a comprehensive, multidisciplinary approach that involves cancer surveillance and consideration of both surgical and medical therapies.

The implementation of such an approach has resulted in increased survival rates for HCC. The therapeutic approach for HCC can vary widely depending on the extent of disease and on the underlying liver impairment due to the cirrhosis: from potentially curative surgical resection and/or ablation for small localized tumors to liver transplantation or newer biologic therapies for more advanced disease. Advances in minimal invasive therapies, such as radiofrequency (RFA), microwaves (MWA) ablation, and transarterial embolization and chemoembolization (TACE/TAE), transarterial radioembolization (TARE), play a vital role in the management of different stages of disease and also in pre- and perioperative transplant patients.

3.3 Staging Systems

Disease staging is particularly important in the management of HCC because it helps to predict prognosis and determine appropriate treatment options. The conventional tumor-node-metastasis (TNM) classification of solid tumors, failed to be considered as reference system as in other fields, because of the two coexisting disease in the liver, even if its prognostic value could be taken in consideration, also for non-operated tumors [9, 10]. The most effective staging systems have to incorporate information about both cancer stage and liver function, which is often affected by the underlying liver disease. The Child-Turcotte-Pugh (CTP = TAB IIa/IIb) model is exclusively an assessment of liver function and is intended to predict prognosis and stratify disease severity, to facilitate transplant allocation [11]. While still used as a complementary tool to help with treatment decisions or evaluate progression and/or regression of disease, the CTP model has largely been replaced by the model for end-stage liver disease (MELD) score [12, 13]. MELD was originally developed at the Mayo Clinic and at that point was called the "Mayo End-stage Liver Disease" score [14]. It was derived from a series of patients undergoing TIPS procedures. The score turned out to be predictive of prognosis in chronic liver disease in general and—with some modifications—came to be applied as an objective tool in assigning need for a liver transplant. Higher MELD scores reflect more severe disease, poorer prognosis, and greater likelihood of liver transplantation, barring any absolute contraindications to transplantation [15–18]. While patients with HCC may be granted exception points that are added to their scores, the MELD system was not designed to assess HCC disease severity, and it does not provide good prognostic classification for these patients. The four major HCC staging systems include the American Joint Committee on

Cancer's tumor-node-metastasis (TNM) model, the Okuda classification model, the Cancer of the Liver Italian Program (CLIP) score, and the Barcelona-Clínic Liver Cancer (BCLC) staging system. The BCLC staging system has emerged as the most accurate and comprehensive cancer model to show consistent prognostic determination. The Barcelona-Clínic Liver Cancer classification divides HCC patients in five stages (0, A, B, C, and D), according to preestablished prognostic variables, and allocates therapies according to treatment-related status (Fig. 3.2) [19–21]. Thus, it provides information on both prognostic prediction and treatment allocation. Prognosis prediction is defined by variables related to tumor status (size, number, vascular invasion, N1, M1), liver function (Child-Pugh's), and health status (ECOG). Treatment allocation incorporates treatment-dependent variables, which have been shown to influence therapeutic outcome, such as bilirubin, portal hypertension, or presence of symptoms-ECOG. While future studies incorporating genomic and proteomic profiles of patients and their cancers will provide even more accurate prognostic data and more individualized therapy, the BCLC model is currently the most comprehensive and widely accepted staging system for HCC, mainly for its practical aspect and for being the only one linked to the treatment algorithm. BCLC has become the reference classification in daily clinical practice and for clinical trials in Western countries, and it is endorsed by EASL (European Associations for the Study of the Liver) and AASLD (American Association for the Study of Liver Diseases). However BCLC stage B and C include a wide range of different tumors even if only referred to TACE as the only therapeutic option. For that reason a complementary score system (NIACE) has been proposed by some experts in order to extend the indications for surgery (BCLC B) or for transarterial chemoembolization (BCLC C) [10] (Tables 3.1 and 3.2).

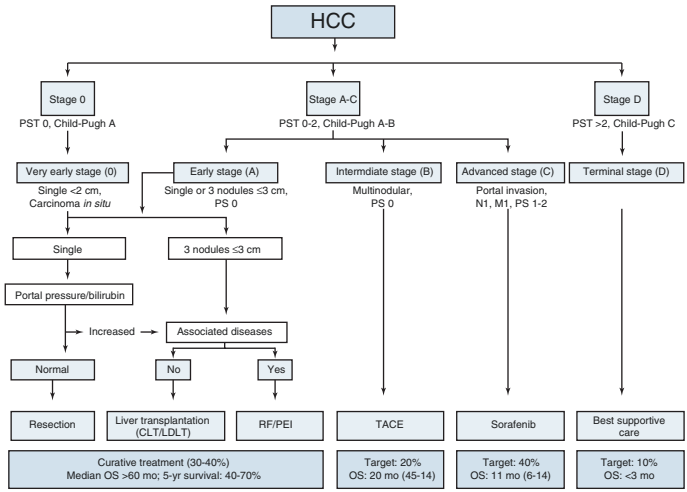

Fig. 3.2 Updated BCLC staging system and treatment strategy, 2011. Reproduced from [22]

Table 3.1 Child Pugh Score System

Measure	1 point	2 points	3 points
Total bilirubin, μmol/L (mg/dL)	<34 (<2)	34–50 (2–3)	>50(>3)
Serum albumin, g/L	>35	28–35	<28
PT INR	<1.7	1.71–2.30	> 2.30
Ascites	None	Mild	Moderate to severe
Hepatic encephalopathy	None	Grade I–II (or suppressed with medication)	Grade III–IV (or refractory)

The score employs five clinical measures of liver disease. Each measure is scored 1–3, with three indicating the most severe liver function impairment [23]

Table 3.2 Child-Pugh score classification

Points	Class	1-year survival (%)	2-year survival (%)
5–6	A	100	85
7–9	B	81	57
10–15	C	45	35

Chronic liver disease is classified into Child-Pugh class A to C, employing the added score from above

3.4 Prognosis

The prognosis of advanced hepatocellular carcinoma (HCC) remains poor, particularly for patients with portal vein tumor thrombosis and extrahepatic metastases (median survival: 3–6 months).

The Tokyo-index is a well established and simple indicator for prognosis for survival.

Tokyo score			
Parameter	0	1	3
Albumin (g/dL)	>3.5	2.8–3.5	<2.8
Bilirubin (mg/dL)	<1	1–2	>2
Tumor size (cm)	<2	2–5	>5
Tumor foci	<3	1–3	>3

Patients with a score up to 2 do have a relative good prognosis. Patients with a total score between 4 and 6 do have a 2-year survival expectation of 50%.

3.5 Therapy

In oncology, the benefits of treatments should be assessed through randomized controlled trials and meta-analysis. Few medical interventions have been systematically tested in HCC,

in contrast with other cancers with a high prevalence worldwide, such as lung, breast, colorectal, and stomach cancer. As a result, the strength of evidence for most therapies in HCC is far behind the most prevalent cancers worldwide. The level of evidence for efficacy, according to trial design and endpoints for all available treatments in HCC and the strength of recommendations according to GRADE, are summarized in Fig. 3.3.

Recommendations, in terms of selection for different treatment strategies, should be based on evidence-based data, in circumstances where all potential efficacious interventions are available. However, multidisciplinary HCC tumor boards, including hepatologists, surgeons, oncologists, radiologists, interventional radiologists, pathologists, and translational researchers, should discuss any single HCC patient, according to the specific clinical characteristics and imaging findings and to the international guidelines; treatment strategies should be adapted to local regulations and/or team capacities and cost-benefit strategies. The ideal treatment option, for a specific

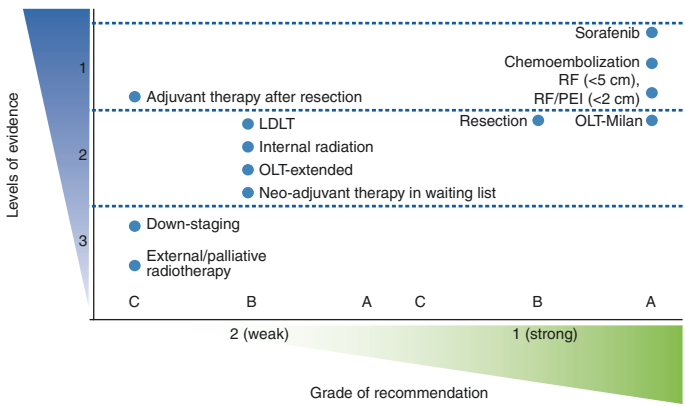

Fig 3.3 Representation of EASL–EORTC recommendations for treatment according to levels of evidence (NCI classification) and strength of recommendation (GRADE system) [24]

patient with HCC, is determined based on the burden of tumor and extent of underlying liver disease.

3.5.1 Surgical Approach

Liver resection or transplantation have been considered the best treatment options, with curative intent, for patients with HCC until the role of hepatic ablative therapies has emerged as effective curative option. A recent meta-analysis of about 8500 patients, with a 10-year perspective, showed that in patients with very early HCC and Child-Pugh class A, RFA provides similar life expectancy and quality-adjusted life year at a lower cost compared with resection [25]. However, surgical resection is still widely considered as the primary treatment in carefully selected patients with HCC. With the advances in surgical and interventional radiology techniques (such as preoperative portal vein embolization), the perioperative mortality has been reduced to less than 5%, depending on the extent of resection and hepatic reserve. Modern standards of HCC resection in cirrhotic patients are defined as follows: expected 5-year survival rates of 60–76%, with a perioperative mortality of 1.3–3% and blood transfusion requirements of less than 10% [26–31]. Anatomic resections, aiming at 2 cm margins, provide better survival outcome than narrow resection margins <1 cm [32] and are recommended only in case that the maintenance of appropriate function to the remnant liver volume is ensured. In patients properly selected according to liver functional status, the main predictors of survival are tumor size, number of microsatellites, and vascular invasion [33].The Japanese nationwide survey has shown that a cutoff below 2 cm is an independent predictor of survival in a series of thousands of patients [34]. Five-year survival rates for patients with HCC ≤2 cm was of 66%, compared with 52% for tumors 2–5 cm, and 37% for tumors >5 cm. Multinodularity also predicts survival, with 5-year survival rates

after resection of single tumors of 57 and 26% for three or more nodules, respectively. A recent meta-analysis, however, demonstrated that OS and DFS were better in hepatic resection with postoperative TACE group than in hepatic resection without postoperative TACE group. The same paper revealed not advantages in using TACE as a neoadjuvant therapy before liver resection [35].

Liver transplantation is the first treatment choice for patients with small multinodular tumors (≤3 nodules ≤3 cm) or those with single tumors ≤5 cm and advanced liver dysfunction. Theoretically, transplantation may simultaneously cure the tumor and the underlying cirrhosis. The role of liver transplantation, as the mainstay of treatment for the majority of patients with HCC, has evolved in the last few decades. Historically, the Milan criteria have been considered the gold standard for selecting patients: single HCC ≤5 cm or up to three nodules ≤3 cm [36]. Following these criteria and according to modern standards, perioperative, 1-year, and 5-year mortality are expected to be 3%, ≤10%, and ≤30%, respectively. Living donor liver transplantation has emerged as a way to expand the donor pool and has influenced the role of transplantation for HCC, especially in communities with little access to cadaveric transplantation. Salvage transplantation is an alternative option as it allows a window for the biologically less favorable lesions to declare tumor behavior. Salvage transplantation also decreases the burden on transplant resources. Three-year survival expectation: 60–80%.

3.5.2 Systemic Therapy

Systemic chemotherapy does not play a central role in the treatment of HCC, due to the issue of a low sensitivity for chemotherapeutic agents and the difficulties in administering a

sufficient dose, due to chronic liver dysfunction. Systemic treatment, by mean of biologicals, is the new frontier for advanced stage HCC. Sorafenib, an oral protein kinase inhibitor, is a systemic drug that has been licensed for the treatment of hepatocellular carcinoma (HCC). An international, phase III, placebo-controlled trial (SHARP) demonstrated an advantage in the median overall survival (10.7 vs. 7.9 months) and the median time to radiological progression (5.5 vs. 2.8 months) Sorafenib group [37].

3.5.3 Minimally Invasive Locoregional Therapies

Locoregional hepatic tumor therapies include intra-arterial, percutaneous, and external therapies and the guidelines of the Liver Cancer Study Group of Japan (JSH 2014), is the only treatment algorithm including all the available local therapeutic techniques, for the wide range of clinical appearances of patients affected by HCC (Fig. 3.4).

Intra-arterial Therapies:

1. Hepatic arterial infusion (HAI)
2. Transarterial chemoembolization (TACE)
3. Transarterial embolization (TAE)
4. Y90 radioembolization (Y90RE)
5. Percutaneous hepatic chemoperfusion (PHP)

Percutaneous Therapies:

1. Percutaneous ethanol injection (PEI)
2. Local ablative techniques (radiofrequency ablation, RFA; microwaves ablation, MWA; laser-induced thermotherapy, LITT)
3. Combined therapies (usually intra-arterial and local ablative)

External Therapies:

1. External Beam Radiation Therapy (EBRT)
2. High-intensity focused ultrasound

Intra-Arterial Therapies:

Clinical conditions:

- Patients with large single or multinodular HCC
- Sufficient liver function
- No infiltration of other big vessels
- No distal metastases influencing the prognosis

3.5.3.1 Hepatic Arterial Infusion (HAI)

Chemotherapeutic agents: 5-Fluorouracile, Cisplatinum/Oxaliplatin, Mitomycin C.

The concept of regional chemotherapy for hepatic metastases via HAI, is based on several principles. First, hepatic tumors (both primary and metastatic ones) derive their blood supply from the hepatic artery, while normal hepatocytes are perfused mostly from the portal circulation [39]. Thus, infusion of chemotherapy via the hepatic artery could achieve toxic levels in tumor cells, with relative sparing of normal hepatic parenchyma. Second, extraction of drug from the hepatic arterial circulation via the first-pass effect, can result in high local concentrations and minimal systemic toxicity. The ideal agent should have a high dose-response curve, high extraction rate, and rapid total body clearance once infusion is discontinued. Intra-arterial chemotherapy is one of the possible treatment options, for patients with advanced HCC not candidate for hepatic resection, percutaneous ablation, and transcatheter arterial chemoembolization. Patients with advanced HCC are increasingly treated in Japan with hepatic

arterial infusion chemotherapy (HAIC). HAIC may provide moderate therapeutic efficacy and survival benefit with substantially tolerable toxicity profiles in patients with advanced HCC.

A dedicated arterial infusion catheter is placed through the left subclavian artery with the tip located into the coiled GDA. A side hole is made, at the level of proper hepatic artery, in order to deliver the drug into the arterial blood stream. Proximal end of infusion catheter is connected with a reservoir (port), which is surgically placed in a subcutaneous pocket, below the clavicle. In BCLC treatment strategy flowchart, selective intra-arterial chemotherapy is not recommended for the management of HCC (**evidence 2A; recommendation 2B**); meanwhile this therapy is indicated by the guidelines of the Liver Cancer Study Group of Japan (JSH 2014) for patients with portal vein invasion at the main portal branch (Fig. 3.4) [38].

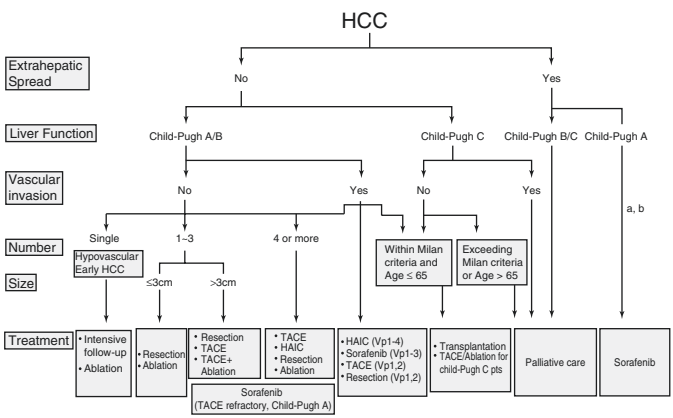

Fig. 3.4 Consensus-based treatment algorithm for hepatocellular carcinoma revised in 2014 [38]

3.5.3.2 Transarterial Chemoembolization (TACE)

Chemotherapeutic agents: Doxorubicin, Cisplatinum, Mitomycin C.

Chemoembolization is the most widely used primary treatment for unresectable HCC [34, 40, 41] and the recommended first-line therapy for patients at intermediate stage of the disease [22, 42, 43]. HCC has an intense neo-angiogenic activity during its progression. The rationale for TACE is that the intra-arterial infusion of a cytotoxic agent, followed by embolization of the tumor-feeding blood vessels, will result in a strong cytotoxic and ischemic effect.

TACE should be distinguished from the lipiodol conventional TACE (cTACE), drug-eluting beads TACE (DEBTACE), and bland embolization (TAE and micro-bland TAE).

– cTACE combines transcatheter delivery of chemotherapy emulsified with lipiodol followed by embolization of the feeding arteries. Chemoembolization achieves partial responses in 15–55% of patients and significantly delays tumor progression and macrovascular invasion. Survival benefits, among supporting care, were obtained for the first time in two studies, both published in 2002 [44, 45].

Meta-analysis of some RCTs showed a beneficial survival effect of TAE/cTACE in comparison to the control group [43]. Sensitivity analysis showed a significant benefit of cTACE with cisplatin or doxorubicin in four studies but none with embolization (using old embolic materials) alone in three studies. Overall, the median survival for intermediate HCC cases is expected to be around 16 months, whereas after chemoembolization the median survival is about 20 months. As a result of these investigations, TACE has been established as the standard of care for patients who meet the criteria for the intermediate stage of the BCLC staging system.

Treatment-related deaths are expected in less than 2% of cases, and the best candidates are patients with preserved liver function and asymptomatic multinodular tumors, without vascular invasion or extrahepatic spread. Patients should present relatively well-preserved liver function (mostly Child-Pugh A or B7 without ascites). Patients with liver decompensation or more advanced liver failure, should be excluded since the ischemic insult can lead to severe adverse events [46], if the technique is not carried out with a super-selective way. There is no good evidence for which is the best chemotherapeutical agent and the optimal re-treatment strategy. Super-selective chemoembolization is recommended to minimize the ischemic insult to non-tumoral tissue, enhancing the therapeutic effect. Hepatic resection, RFA, and cTACE have been recently compared regarding the long-term survival, and it was found that a 5-year OS with cTACE was similar to the other two local treatments, in patients with single-nodule HCC of 3 cm or smaller without vascular invasion. The authors also suggested that special care should be taken to obtain a complete response when cTACE is used as an initial treatment [47]. cTACE, DEBTACE, and TAE are usually performed through the femoral artery percutaneous approach. A selective angiography of proper hepatic artery has to be performed, in order to define the liver vasculature and detect the tumor-feeding vessels. With the help of selective catheters and micro-catheters, a super-selective embolization of tumor-feeding arteries should be achieved, sparing the unaffected areas of the liver parenchyma. Endpoint, for a better result, should be the vascular shutdown to the tumor. Despite selecting the patients and performing a super-selective embolization, TACE is not without risks. Complications may range from post-embolization syndrome (of variable intensity) to liver abscesses, hepatic insufficiency, ischemic cholecystitis, or cases of death that have even been also described. The use of cone-beam CT or fluoro-CT hybrid devices during the intra-arterial techniques, also

can improve the efficacy and safety of chemoembolization, positively affecting the prognosis of HCC patients [48].

– DEBTACE. The ideal TACE scheme should allow maximum and sustained intratumoral concentration of the chemotherapeutic agent with minimal systemic exposure, along with calibrated tumor vessel obstruction. DEBTACE is performed by injecting microspheres loaded with antiblastic drug, such as doxorubicin. Unlikely to the cTACE, where the injected drug is quickly release into the systemic circulation, drug-eluting beads provide a gradual release of the chemotherapy agent into the tumor, reducing the systemic side effect and maximizing the local efficacy against tumor cells. Embolic microspheres have the ability to sequester chemotherapeutic agents and release them in a controlled mode, over a 1-week period. This strategy has been shown to increase the local concentration of the drug, with negligible systemic toxicity [49]. However, a randomized phase II study comparing TACE and DEBTACE reported a nonsignificant trend of better antitumoral effect [50] [295r] in the latter arm. Two recent meta-analyses comparing DEBTACE with cTACE concluded that both techniques lead to similar clinical response and tolerance [51, 52].

3.5.3.3 Transarterial Embolization (TAE)

In the majority of published studies on HCC treatment with TAE, the reported embolic agent is gelatin sponge, which may induce only temporarily ischemia and without distal tumor vessel embolization. Only recently, few new studies on new embolic agents, such as resin or gelatin microspheres, are available. Even if there is no evidence for a better survival benefit from DEBTACE than TACE and also TAE, if performed with

small particles (40/100 μm), there is an increasing general consensus about the need to use the smallest available particles in treating HCC, in order to achieve a better, durable, and deeper embolic effect, independently by the use of drug or not [53–56]. Few papers on HCC treatment with TAE, using very small particles, reported an interesting safety profile with local results comparable with DEBTACE/TACE series [57]. A retrospective study, comparing TAE and DEBTACE in patients waiting for liver transplantation, demonstrated no differences in outcomes of the two treatments [58]. However, based on data coming from old papers on TAE with gelatin sponge, **BCLC doesn't recommend the use of TAE for HCC.** A recent randomized clinical trial comparing TAE and DEBTACE reported no apparent difference, between the two treatment arms, in terms of response, PFS, or OS. The authors also supported the use of TAE as a reasonable therapeutic option and an alternative to the DEBTACE with doxorubicin-loaded microspheres, according to the comparable safety profile, progression rate, and survival [59].

3.5.3.4 Y90 Radio Embolization (Y90RE)

Radioembolization is defined as the infusion of very small (<40 μm) microspheres containing yttrium-90 (90Y) [60–62] into the hepatic artery. Due to the hypervascularity of HCC, intra-arterial injection of microspheres will be preferentially delivered to the tumor-bearing area and selectively emit high energy, with a low-penetrating radiation to the tumor. This treatment should be reserved only to centers with sophisticated equipments and trained interventional radiologists, in cooperation with nuclear medicine specialists, in order to reduce the potential risk of possible serious side effects: severe lung shunting and intestinal radiation should be prevented prior to the procedure. This treatment can be safely used in patients with portal

vein thrombosis, where it seems to obtain the best clinical results [61]. Recently, some studies reported a median survival time of 17.2 months for patients at intermediate stages and 12 months for patients at advanced stages and portal vein invasion [61–63]. Objective response rates ranged from 35 to 50% [60–62]. Around 20% of patients present liver-related toxicity and 3% treatment-related death [60]. Despite the amount of data reported, there are no RCT testing the efficacy of 90Y radioembolization compared with chemoembolization or sorafenib in patients at intermediate or advanced stage, respectively. Only retrospective analyses are available, reporting approximately equivalent survivals after TACE and TARE. However, in a recent meta-analysis, the adjusted indirect comparison of DEBTACE versus TARE for hepatocellular carcinoma revealed a median overall survival longer for DEBTACE (22.6 vs. 14.7 months), with no significant difference in tumor response rate [64].

Further research trials are needed to establish a competitive efficacy role in this population **(BCLC = evidence 2A; recommendation 2B).**

3.5.3.5 Percutaneous Hepatic Chemoperfusion (PHP)

Percutaneous hepatic perfusion (PHP) is a regionalized, minimally invasive approach to cancer treatment currently undergoing Phase II and Phase III clinical testing in melanoma, CRC, and NET metastatic patients. PHP may treat a variety of hepatic tumors, including HCC, by isolating the liver and exposing the organ to high-dose chemotherapy [65]. As demonstrated in clinical trials, patients treated by PHP can tolerate much higher doses of chemotherapeutic agents than those receiving traditional systemic chemotherapy without increased toxicities.

Using a system of catheters and filters, PHP isolates the liver from the circulatory system and infuses a chemotherapeutic agent directly to the liver via the hepatic artery. The venous efflu-

ent from the liver is then filtered outside of the body, and the filtered blood is returned into the jugular vein. PHP is a repeatable procedure and can be performed in an operating room or a radiology suite under general anesthesia. There are very few experiences in the treatment of HCC patients; however the complexity of this revolutionary technique represents the main limitation. Further studies and a longer experience are needed before to treat HCC patient with PHP outside protocol studies.

3.5.4 *Study Results: Neoadjuvant Therapies (HAI/Chemoembolization)*

Author	*N*	Concept[a]	Intra-arterial therapy	RR (%)	Median survival (months)	Years survival (%)
Gerunda et al. [66]	89	TACE + LR vs. LR vs. TACE	1×: 50 mg epirubicin + Gelfoam	ND	Overall survival: TACE + LR vs. TACE/LR: $p < 0.05$	1 year: 85 vs. 71 vs. 68 5 years: 43 vs. 38 vs. 0
Graziadei et al. [67]	48	TACE + LT	70 mg epirubicin + lipiodol (+/−PVA particles) Every 6–8 weeks	CR: 30 PR: 67	ND	1 year: 98 2 years: 98 5 years: 94
Yao et al. [68]	30	TACE+/− RFA+/− PEI + LT	ND	Down staging: 70	ND	1 year: 89 2 years: 82
Bharat et al. [69]	100	TACE (78%), RFA (11%), PEI (2%), TACE + RFA (9%) + LT vs. LT	50 mg cisDDP + 20 mg doxorubicin + 10 mg MMC + particles every 4–6 weeks	Path RR: significant advantage for neoadjuvant therapy	5y OS(%): 82 vs. 52 (no difference in pT0 and pT1)	ND

(continued)

(continued)

Author	*N*	Concept[a]	Intra-arterial therapy	RR (%)	Median survival (months)	Years survival (%)
Obed et al. [70]	74	TACE + LT vs. TACE vs. No therapy	50 mg epirubicin + lipiodol Every 6 weeks	After TACE: 29 PD: 70	92 vs. 8 vs. 4	ND
Zangos et al. [71]	48	TACE + LITT	10 mg/m^2 MMC + lipiodol + DSM 3× every 4 weeks	CR: 67 SD: 25 PD: 8	36	ND
Hoffmann et al. [72]	208	TACE +/− sorafenib + LT	4× carbo-DDP + lipiodol			
Zhou et al. [73]	108	TACE vs. control	3× 1000 mg 5-FU + 20 mg MMC + 5 mg cisDDP + lipiodol Every 4–9 weeks	Path. RR: ≤50%: 40.4 vs. 94.6 50–100%: 59.6 vs. 5.4 ($p < 0.01$)	ND	DfS (1 year, 3 years, 5 years): 49, 26, 13 vs. 39, 21, 9 OS (1 year, 3 years, 5 years): 73, 40, 31 vs. 70, 32, 21 $p > 0.05$
Choi et al. [74]	16	TACE + radiation + LR	50 mg doxorubicin + lipiodol + Gelfoam Median: 3×/ patient	12 CR: 0 PR: 2 PD: 3	13	ND
Schaudt et al. [75]	27	TACE/TACE + PEI/ LITT + LT	10 mg MMC + lipiodol + DSM Every 3–6 weeks	TACE ($N = 15$): PR/SD: $N = 14$	OS (TACE vs. non-TACE): 82 vs. 61%	ND
Wang et al. [76]	MA 257	TACE + LR vs. LR	cTACE	ND	ND	5y OS = in two groups

(continued)

Author	*N*	Concept[a]	Intra-arterial therapy	RR (%)	Median survival (months)	Years survival (%)
Yu et al. [77]	MA 1347	TACE + LR vs. LR	cTACE	5y DFS > in TACE + LR	ND	ND
Si et al. [78]	MA 430	TACE + LR vs. LR	cTACE	ND	ND	5y OS = in two groups

[a]*LR* liver resection, *LT* liver transplantation, *RFA* radiofrequency ablation, *LITT* laser-induced thermotherapy, *MA* meta-analysis

3.5.5 *Study Results: Adjuvant Therapy (HAI/ Chemoembolization)*

Author	*N*	Concept	Intra-arterial therapy	Median survival (months)	Years survival/DfS (%)
Lai et al. [79]	66	LR + TACE + IV chemotherapy vs. LR (control)	3 × 10 mg cisDDP + lipiodol + 40 mg/m^2 doxorubicin IV every 2 months	ND	DfS (1, 2, 3 years): 50, 36, 18 vs. 69, 53, 48 ($p = 0.04$)
Ono et al. [80]	108	HAI/IV vs. control (meta-analysis of 3 protocols)	1. 1 × 40 mg/m^2 epirubicin + oral 300 mg/d tegafur vs. control 2. 1 × 40 mg/m^2 epirubicin + IV 40 mg/m^2 epirubicin every 3 months +300 mg/day Carmofur (2 years) vs. control 3. IV 40 mg/m^2 epirubicin every 2 months (1 year) vs. control	OS: significant advantage in patients without adjuvant treatment $p = 0.02$	DfS (3, 5 year): 37, 28 vs. 42, 26 $p = 0.324$

(continued)

(continued)

Author	*N*	Concept	Intra-arterial therapy	Median survival (months)	Years survival/DfS (%)
Wen et al. [81]	28	LR + HAI	d1: 250 mg FUDR d4: 10 mg doxorubicin d7: 4 mg MMC 8 cycles (1st and 2nd year after resection)	ND	1 year: 11 3 years: 7 5 years: 5
Li et al. [82]	131	A: LR vs. B: LR + TACE vs. C: LR + TACE + PVC[a]	3 × 30 mg doxorubicin + 20 mg mitomycin +80–100 mg cis- or carbo-DDP + lipiodol	ND	DfS (1, 3, 5 year): 87, 66, 48 vs. 87, 77, 61 vs. 96, 85, 73 A vs. C: $p = 0.005$ A vs. B and B vs. C: $p > 0.05$
Peng et al. [83]	116	TACE vs. control	500 mg/m^2 5-FU + 30 mg/m^2 doxorubicin + lipiodol + Gelfoam (2–5 cycles monthly)	13 vs. 9	Estimated survival rates (1, 3, 5 years): 51, 34, 22 vs. 33, 17, 9
Zhou et al. [73]	115	LR + TACE vs. LR	200 mg/m^2 carbo-DDP + 6 mg/m^2 MMC + lipiodol + 40 mg/m^2 epirubicin	14 vs. 23	OS (1, 3, 5 years): 56, 19, 18 vs. 81, 33, 23
Zhong et al. [84]	659	LR + TACE vs. LR (meta-analysis)	Doxorubicin, epirubicin, MMC, 5-FU, carbo-DDP + lipiodol +/− Gelfoam	49 vs. 41 (15 vs. 9 for patients with palliative LR)	ND
Cheng et al. [85]	909	(MA) LR + TACE vs. LR	Doxorubicin, epirubicin, MMC, 5-FU, carbo-DDP + lipiodol +/− Gelfoam	ND	5y OS/DFS > in TACE + LR group

[a]*PVC* portal vein chemotherapy

3.5.6 Study Results: Palliative Therapy

Llovet et al. (2002) [45]:

Concept	TAE vs. TACE vs. BSC
N	112 (37 vs. 40 vs. 35)
Therapy	TA(C)E: Gelfoam +/−75, 50 oder 25 mg/m^2 doxorubicin + Lipiodol
Frequency	Every 2 and 6 month, then every 6 month
Median survival (month)	25 vs. 29 vs. 18
	1, 2, 3 year (%): 75, 50, 29 vs. 82, 63, 29 vs. 17, 0, 0 ($p = 0.009$)
Toxicity ($N \geq$ grade III)	TAE: 7 vs. TACE: 11 (cholecystitis, ischemic hepatitis, liver abscess, liver failure, gastrointestinal bleeding)
Conclusion	Therapeutic advantage for TACE, comparable results for TAE and BSC. Chemoembolization is the therapeutic standard for patients with unresectable HCC with adequate liver functions

Furuse et al. (2003) [86]:

Concept	TACE
N	17
Access	Via A. femoralis (A. hepatica distal of A. gastroduodenalis, left or right)
Therapy	40 mg/m^2 epirubicin + Amilomer (DSM)
Frequency	Every 4–6 weeks
Response (%)	RR: 53
Median survival	22 month
	2 year (%): 45
Toxicity (%)	pain (44), nausea (44), vomiting (22), fever (44), leucopenia (44)
Conclusion	In opposite to a lot of other TACE studies with nondegradable embolic materials, severe toxicities were not seen in this one. The promising response rates have to be reevaluated in bigger randomized studies

Huo et al. (2003) [87]:

Concept	TACE + PAI vs. PAI
N	108
Therapy	TACE: 20–30 mg doxorubicin + lipiodol + Gelfoam PAI: 50% acetic acid
Frequency	TACE + PAI: max. 3× PAI: 2×/week
Median survival	1–3 year: TACE + PAI vs. PAI: 100, 69 vs. 96, 32 ($p = 0.008$)
Toxicity (%)	TACE: fever, pain, elevation of liver enzymes (most of patients) PAI: mild
Conclusion	Sequential therapy with TACE and PAI is superior to repeated PAI therapies alone

Dettmer et al. (2006) [88]:

Concept	(1) TACE + PEI vs. (2) PEI vs. (3) PEI after TACE vs. (4) PEI after BSC
N	101
Therapy	PEI: 96% steriler Äthanol TACE: 50 mg/m^2 cisDDP +50 mg/m^2 Doxorubicin +450–900 mg Amilomer (DSM) + 5–30 mL lipiodol
Frequency	ND
Median survival	1, 3 year: 73%, 47% 1, 3, 5 year (%):(1): 90, 52, 43 ($N = 37$)/(2): 65, 50, 37 ($N = 34$)/(3): 91, 40, 30 ($N = 10$)/(4): 50, 23, 12 ($N = 20$) (1) vs. (4) $p < 0.001$
Toxicity (%)	TACE ($N = 67$): 10.4% (2× leukopenia, 1× pancytopenia, 2× dissection of A. hepatica, 1× liver failure (reversible), 1× inguinal hematoma) PEI ($N = 268$): 25.7%
Conclusion	Patients stratified to a combination of TACE and PEI can expect longer survival than those stratified to repeated PEI alone. Furthermore, patients with large or multiple tumors in good clinical status may also profit from a combination of TACE and reconsideration for secondary PEI

Takayasu et al. (2006) [41]:

Concept	Prospective cohort study of TACE
N	8510
Therapy	Doxorubicin + cisDDP + lipiodol + Gelfoam
Frequency	ND
Median survival	1-, 3-, 5- und 7-Jahresüberleben (*N* = 8510): 82%, 47%, 26%, 16% Stadium T2 1-, 3- und 5-Jahresüberleben (*N* = 2934): 90%, 57%, 32% Stadium T3 1-, 3- und 5-Jahresüberleben (*N* = 2949): 80%, 39%, 20% Medianes Überleben 34 Monate
Toxicity	Mortality of TACE: 0.5%
Conclusion	TACE showed safe therapeutic modality with a relatively high 5-year survival rate for unresectable HCC patients

Kirchhoff et al. (2007) [89]:

Concept	Retrospective cohort study of TACE
N	47
Therapy	50 mg/m^2 cisDDP + 50 mg/m^2 doxorubicin +450–900 mg Amilomer (DSM) + lipiodol
Frequency	Every 6 weeks
Response	CR: 0, PR: 36%, NC: 55%, PD: 9%
Median survival	1 year, 2 year, 3 year: 75%, 59%, 41% OS 26 month
Toxicity (%)	Grad III: 7.1% (*N* = 8), Grad IV: 3.6% (*N* = 4),
Conclusion	DSM and lipiodol were combined successfully in the palliative TACE treatment of advanced HCC resulting in high rates of tumor response and survival at limited toxicity

Ishida et al. (2008) [90]:

Concept	TACE after TAE
N	13
Therapy	d1: 4–8 mg MMC + DSM followed by 1250 mg 5-FU + 25–50 mg cisDDP 125 mg FA d7: 1250 mg 5-FU + 25–50 mg cisDDP 125 mg FA
Frequency	Every 2 weeks
RR	CR: 1, PR: 12 RR: 86.7%
Survival	1-, 2, 3 year (%): 100, 29, 10 Median survival (month): 20.4
Toxicity (N)	Thrombocytopenia (> grade III): 8, abdominal pain (grade I–III): most of the patients, duodenal ulcer (II + III): 3
Conclusion	This novel TACE concept achieves favorable results and is useful in treating patients with multifocal HCC

Salem et al. (2010) [60]:

Concept	HAI of ^{90}Y (single-center prospective)
N	291
Therapy	1–5 dosages (100–120 Gy/therapy), glass–based device
Results	TTP: 8 months OS (BCLC B vs. Child-Pugh A): 17 vs. 14 months RR (CR, PR): 42%
Toxicity	Bilirubin (grade III + IV): 19%, fatigue: >50%, diarrhea (some)
Conclusions	Patients with Child-Pugh A disease, with or without PVT, benefited most from the therapy. Patients with Child-Pugh B disease who had PVT had poor outcomes. These data can be used to design future Y90 trials and to describe Y90 as a potential treatment option for patients with HCC

Carr et al. (2010) [91]:

Concept	Comparison of TACE and HAI ^{90}Y (single-center 2 cohort experience analyses, retrospectively)
N	932
Inclusion criteria	No candidates for surgical resection, RFA, or hepatic transplantation
Therapy	TACE (catheter): 125 mg/m^2 cisDDP (30 min) + dexamethasone Embolization: Gelfoam or embospheres (100–300$_{/}$µm) Every 8–12 weeks HAI ^{90}Y: Single dose (after early progress second treatment possible)
Results	TACE ($N = 691$), HAI ^{90}Y ($N = 99$), no treatment ($N = 142$) OS: 8.5 (TACE), 11.5 (HAI ^{90}Y), 2.0 (untreated) RR (CR, PR, SD): 89% (TACE), 76 (HAI ^{90}Y) RR (%): 65; PfS: 10.5 months, CR: $N = 3$, PR: $N = 8$; OS: 27.5 months
Toxicity (HAI)	Hematological (grade III + IV): $N = 9$, non-hematological (grade II + IV): $N = 4$
Conclusions	^{90}Y and TACE seem to be equivalent regional therapies for patients with unresectable HCC

Lammer et al. (2010) [50]:

Concept	Comparison of doxorubicin-eluting-bead embolization with TACE
N	212
Therapy	4 mL DC beads (2 vials) with 150 mg doxorubicin vs. 50–75 mg/m^2 doxorubicin + lipiodol + particles (e.g., PVA, Gelfoam)
Frequency	Every 2 months
RR (at 6 months)	DC beads: CR: 27, PR: 25 TACE: CR: 22, PR: 21 RR (%): 52 vs. 44 ($p = 0.11$)
Survival	ND
Toxicity (*N*)	No statistical difference for primary safety endpoints
Conclusion	DC bead embolization leads to lower systemic doxorubicin levels with less systemic side effects. The activity is comparable to classical TACE

Nagano (2010) [92]:

Concept	HAI + IFN-α (s.c.)
N	55
Therapy	d1–5, 8–12: 300 mg/mm^3/d 5-FU + 3x/week 5 Mio IU IFN-α (s.c.) week 3 and 4: only IFN
Frequency	1×
RR	CR: 8, PR: 4 RR: 44%
Survival	1 year, 3 years (responders): 83, 31 Median survival (months): 12
Toxicity (*N*)	Fever, chills, flue-like syndrome (grade I + II) Fatigue, nausea (grade I)
Conclusion	This therapy might be a promising strategy for patients with advanced HCC

Kucuk et al. (2010) [93]:

Concept	Comparison of TACE and HAI ^{90}Y (single-center 2 cohort experience analyses, retrospectively)
N	932
Inclusion criteria	No candidates for surgical resection, RFA, or hepatic transplantation
Therapy	TACE (catheter): 125 mg/m^2 cisplatin (30 min) + dexamethasone Embolization: Gelfoam or embospheres (100–300 μm) Every 8–12 weeks HAI ^{90}Y: Single dose (after early progress second treatment possible)
Results	TACE (*N* = 691), HAI ^{90}Y (*N* = 99), no treatment (*N* = 142) OS: 8.5 (TACE), 11.5 (HAI ^{90}Y), 2.0 (untreated) RR (CR, PR, SD): 89% (TACE), 76 (HAI ^{90}Y) RR (%): 65; PfS: 10.5 month, CR: *N* = 3, PR: *N* = 8; OS: 27.5 month
Toxicity (HAI)	Hematological (grade III + IV): *N* = 9, non-hematological (grade II + IV): *N* = 4
Conclusions	^{90}Y and TACE seem to be equivalent regional therapies for patients with unresectable HCC

Kondo et al. (2011) [94]:

Concept	HAI
N	24 with portal vein tumor thrombosis
Therapy	65 mg/m^2 cisDDP (in 70 mL)
Frequency	Every 4–6 weeks
RR	CR: 1, PR: 4 RR: 21%
Survival	1 year, 2 year (%): 38, 16 OS: 7 months
Toxicity (*N*)	Anorexia, nausea, fatigue, liver enzymes (grade III + IV)
Conclusion	Safe and well-tolerated therapy for this special group of patients

Gao et al. (2016) [95]:

Concept	TACE vs. TACE + HAI
N	29 TACE vs. 45 TACE + HAI
Therapy	TACE = 40 mg epirubicin; HAI = OXA + CF + 5FU
Frequency	Every 4–6 weeks
RR	TACE = ORR 45.9%; DCR 70.3% TACE + HAI = ORR 68.9%; DCR 86.7%
Survival	mPFS = 8 month (TACE + HAI) vs. 4.5 month (TACE)
Toxicity (*N*)	More common in TACE + HAI
Conclusion	TACE + HAI may be safe and more effective than TACE alone for inoperable HCC

Bonomo et al. (2010) [57]:

Concept	mbTAE = micro-bland embolization
N	66 patients with HCC (single or multiple nodules)
Therapy	Microparticles (40 and/or 100 μm) injection until blood shut down
Frequency	On demand, according to the imaging follow-up
Results (RECIST)	OR (CR + PR) = 58% DS (OR + SD) = 76%
Survival	1 year, 2 year (%): 96, 92
Toxicity (*N*)	No/very low Post Embolization Syndrome
Conclusion	Safe and well-tolerated therapy with very high local results and survival benefits

Brown et al. (2016) [59]:

Concept	TAE vs. DC beads in HCC
N	51 pts. TAE vs. 50 pts. DC beads
Therapy	Microparticles (100–300 μm) without drug (TAE) or with doxo (DC beads)
Frequency	On demand, according to the imaging follow-up @ 3 months
Results (RECIST)	No difference between TAE and DC beads in any measure, including PFS or response rate, at any time point
Toxicity (*N*)	No difference
Conclusion	TAE should continue to be considered a reasonable therapeutic option and an alternative to embolization with doxorubicin-loaded microspheres

Ibrahim et al. (2011) [96]:

Concept	Down staging of HCC with ^{90}Y (single center, prospectively)
N	8
Inclusion criteria	HCC with involved caudate lobe
Therapy	Single dose mostly (range 1–3)
Results	CR: $N = 1$ (WHO), $N = 3$ (EASL guidelines) OS: 25 months (censored) PfS: 10 months
Toxicity	Fatigue: 50%, bilirubin (grade III): $N = 1$
Conclusions	^{90}Y appears to be a feasible, safe, and effective treatment with unresectable caudate lobe HCC

Zhang et al. (2015) [97]:

Concept	TARE vs. TACE (meta-analysis)
N	(8 studies) 1499 pts.: 1048 TACE and 451 TARE for HCC
Inclusion criteria	Unresectable HCC in child A patients
Results	3 year OS better in TARE groups

Toxicity	No statistical difference between groups on any complications
Conclusions	Due to a better 3-year OS, TTP, hospitalization time, and some complications, the use of TARE (Y90) for HCC patients is to be considered promising

Lobo et al. (2016) [98]:

Concept	TARE vs. TACE (meta-analysis)
N	(5 studies) 553 pts.: 284 TACE and 269 TARE for HCC
Inclusion criteria	Unresectable HCC
Results	4 year OS no difference; CR and PR no difference
Toxicity	No difference in fever, nausea, and vomiting
Conclusions	TARE appears to be a safe alternative treatment to TACE in patients affected by unresectable HCC

References

1. IARC. Globocan Estimated cancer Incidence, Mortality, Prevalence and Disability-adjusted life years (DALYs) Worldwide in 2008. 2011. http://www-dep.iarc.fr/. Accessed 1 Nov 11.
2. El-Serag HB, Mason AC. Rising incidence of hepatocellular carcinoma in the United States. N Engl J Med. 1999;340:745–50.
3. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. CA Cancer J Clin. 2002;55:74–108.
4. Sangiovanni A, Prati GM, Fasani P, Ronchi G, Romeo R, Manini M, Del Ninno E, Morabito A, Colombo M. The natural history of compensated cirrhosis due to hepatitis C virus: A 17-year cohort study of 214 patients. Hepatology. 2006;43:1303–10.
5. Ripoll C, Groszmann RJ, Garcia-Tsao G, Bosch J, Grace N, Burroughs A, Planas R, Escorsell A, Garcia-Pagan JC, Makuch R, Patch D, Matloff DS. Hepatic venous pressure gradient predicts development of hepatocellular carcinoma independently of severity of cirrhosis. J Hepatol. 2009;50:923–8.

6. Masuzaki R, Tateishi R, Yoshida H, Goto E, Sato T, Ohki T, Imamura J, Goto T, Kanai F, Kato N, Ikeda H, Shiina S, Kawabe T, Omata M. Prospective risk assessment for hepatocellular carcinoma development in patients with chronic hepatitis C by transient elastography. Hepatology. 2009;49:1954–61.
7. Jung KS, Kim SU, Ahn SH, Park YN, Kim DY, Park JY, Chon CY, Choi EH, Han K-H. Risk assessment of hepatitis B virus-related hepatocellular carcinoma development using liver stiffness measurement (FibroScan). Hepatology. 2011;53:885–94.
8. Bruix J, Sherman M, Llovet JM, Beaugrand M, Lencioni R, Burroughs AK, Christensen E, Pagliaro L, Colombo M, Rodés J. Clinical management of hepatocellular carcinoma. Conclusions of the Barcelona-2000 EASL conference. European Association for the Study of the Liver. J Hepatol. 2001;35:421–30.
9. Kee KM, Wang JH, Lee CM, Chen CL, Changchien CS, Hu TH, Cheng YF, Hsu HC, Wang CC, Chen TY, Lin CY, Lu SN. Validation of clinical AJCC/UICC TNM staging system for hepatocellular carcinoma: analysis of 5,613 cases from a medical center in southern Taiwan. Int J Cancer. 2007;120:2650–5.
10. Adhoute X, Penaranda G, Raoul JL, Le Treut P, Bollon E, Hardwigsen J, Castellani P, Perrier H, Bourlière M. Usefulness of staging systems and prognostic scores for hepatocellular carcinoma treatments. World J Hepatol. 2016;8(17):703–15.
11. Christensen E, Schlichting P, Fauerholdt L, Gluud C, Andersen PK, Juhl E, Poulsen H, Tygstrup N. Prognostic value of Child-Turcotte criteria in medically treated cirrhosis. Hepatology. 1984;4:430–5.
12. Wiesner R, Edwards E, Freeman R, Harper A, Kim R, Kamath P, Kremers W, Lake J, Howard T, Merion RM, Wolfe RA, Krom R. Model for end-stage liver disease (MELD) and allocation of donor livers. Gastroenterology. 2003;124:91–6.
13. Ravaioli M, Grazi GL, Ballardini G, Cavrini G, Ercolani G, Cescon M, Zanello M, Cucchetti A, Tuci F, Del Gaudio M, Varotti G, Vetrone G, Trevisani F, Bolondi L, Pinna AD. Liver transplantation with the Meld system: a prospective study from a single European center. Am J Transpl. 2006;6:1572–7.
14. Mayo End-Stage Liver Disease Score. www.mayoclinic.org/meld/mayomodel6.html. Accessed 20 Mar 2013.
15. Freeman RB, Edwards EB. Liver transplant waiting time does not correlate with waiting list mortality: implications for liver allocation policy. Liver Transpl. 2000;6:543–52.

16. Institute of Medicine. Analysis of waiting times. In: Organ Procurement and Transplantation: Current Policies and the Potential Impactof the DHHS Final Rule. Washington, DC: National Academy Press; 1999.
17. Organ Procurement and Transplantation Network-HRSA. Final rule with comment period. Fed Regist. 1998;63(63):16296–338.
18. Freeman RB, Wiesner RH, Harper A, McDiarmid SV, Lake J, Edwards E, Merion R, Wolfe R, Turcotte J, Teperman L. The new liver allocation system: moving toward evidence-based transplantation policy. Liver Transpl. 2002;8:851–8.
19. Llovet JM, Brú C, Bruix J. Prognosis of hepatocellular carcinoma: the BCLC staging classification. Semin Liver Dis. 1999;19:329–38.
20. Cillo U, Vitale A, Grigoletto F, Farinati F, Brolese A, Zanus G, Neri D, Boccagni P, Srsen N, D'Amico F, Ciarleglio FA, Bridda A, D'Amico DF. Prospective validation of the Barcelona Clinic Liver Cancer staging system. J Hepatol. 2006;44:723–31.
21. Wong R, Frenette C. Updates in the management of hepatocellular carcinoma. Gastroenterol Hepatol (N Y). 2011;7:16–24.
22. Llovet JM, Di Bisceglie AM, Bruix J, Kramer BS, Lencioni R, Zhu AX, Sherman M, Schwartz M, Lotze M, Talwalkar J, Gores GJ. Design and endpoints of clinical trials in hepatocellular carcinoma. J Natl Cancer Inst. 2008;100:698–711.
23. Avunduk C, Eastwood GL. Manual of gastroenterology, diagnosis and therapy. 2nd ed. Boston, MA: Little Brown and Company; 1994. p. 415–7.
24. European Association for the Study of the Liver; European Organisation for Research and Treatment of Cancer. EASL_EORT Clinical Practice Guidelines: management of hepatocellular carcinoma. J Hepatol. 2012;56(4):908–43.
25. Cucchetti A, Piscaglia F, Cescon M, Colecchia A, Ercolani G, Bolondi L, Pinna AD. Cost-effectiveness of hepatic resection versus percutaneous radiofrequency ablation for early hepatocellular carcinoma. J Hepatol. 2013;59(2):300–7.
26. Llovet JM, Bruix J. Novel advancements in the management of hepatocellular carcinoma in 2008. J Hepatol. 2008;48(Suppl 1):S20–37.
27. Roayaie S, Blume IN, Thung SN, Guido M, Fiel M-I, Hiotis S, Labow DM, Llovet JM, Schwartz ME. A system of classifying microvascular invasion to predict outcome after resection in patients with hepatocellular carcinoma. Gastroenterology. 2009;137:850–5.
28. Poon RTP, Fan ST, Lo CM, Liu CL, Lam CM, Yuen WK, Yeung C, Wong J. Extended hepatic resection for hepatocellular carcinoma in patients with cirrhosis: is it justified? Ann Surg. 2002;236:602–11.

29. Mazzaferro V, Romito R, Schiavo M, Mariani L, Camerini T, Bhoori S, Capussotti L, Calise F, Pellicci R, Belli G, Tagger A, Colombo M, Bonino F, Majno P, Llovet JM. Prevention of hepatocellular carcinoma recurrence with alpha-interferon after liver resection in HCV cirrhosis. Hepatology. 2006;44:1543–54.
30. Ishizawa T, Hasegawa K, Aoki T, Takahashi M, Inoue Y, Sano K, Imamura H, Sugawara Y, Kokudo N, Makuuchi M. Neither multiple tumors nor portal hypertension are surgical contraindications for hepatocellular carcinoma. Gastroenterology. 2008;134:1908–16.
31. Margonis GA, Sasaki K, Andreatos N, Nishioka Y, Sugawara T, Amini N, Buettner S, Hashimoto M, Shindoh J, Pawlik TM. Prognostic impact of complications after resection of early stage hepatocellular carcinoma. Surg Oncol. 2017;15(7):791–804.
32. Shi M, Guo R-P, Lin X-J, Zhang Y-Q, Chen M-S, Zhang C-Q, Lau WY, Li J-Q. Partial hepatectomy with wide versus narrow resection margin for solitary hepatocellular carcinoma: a prospective randomized trial. Ann Surg. 2007;245:36–43.
33. Llovet JM, Schwartz M, Mazzaferro V. Resection and liver transplantation for hepatocellular carcinoma. Semin Liver Dis. 2005;25:181–200.
34. Ikai I, Arii S, Kojiro M, Ichida T, Makuuchi M, Matsuyama Y, Nakanuma Y, Okita K, Omata M, Takayasu K, Yamaoka Y. Reevaluation of prognostic factors for survival after liver resection in patients with hepatocellular carcinoma in a Japanese nationwide survey. Cancer. 2004;101:796–802.
35. Qi X, Liu L, Wang D, Li H, Su C, Guo X. Hepatic resection alone versus in combination with pre- and post-operative transarterial chemoembolization for the treatment of hepatocellular carcinoma: a systematic review and meta-analysis. Oncotarget. 2015;6(34):36838–59.
36. Mazzaferro V, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F, Montalto F, Ammatuna M, Morabito A, Gennari L. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med. 1996;334:693–9.
37. Rimassa L, Santoro A. Sorafenib therapy in advanced hepatocellular carcinoma: the SHARP trial. Expert Rev Anticancer Ther. 2009;9(6):739–45.
38. Kudo M, Matsui O, Izumi N, Iijima H, Kadoya M, Imai Y, Okusaka T, Miyayama S, Tsuchiya K, Ueshima K, et al. JSH Consensus-based clinical practice guidelines for the Management of Hepatocellular Carcinoma: 2014 update by the Liver Cancer Study Group of Japan. Liver Cancer. 2014;3(3–4):458–68.
39. Breedis C, Young G. The blood supply of neoplasms in the liver. Am J Pathol. 1954;30:969–77.

40. Arii S, Yamaoka Y, Futagawa S, Inoue K, Kobayashi K, Kojiro M, Makuuchi M, Nakamura Y, Okita K, Yamada R. Results of surgical and nonsurgical treatment for small-sized hepatocellular carcinomas: a retrospective and nationwide survey in Japan. The Liver Cancer Study Group of Japan. Hepatology. 2000;32:1224–9.
41. Takayasu K, Arii S, Ikai I, Omata M, Okita K, Ichida T, Matsuyama Y, Nakanuma Y, Kojiro M, Makuuchi M, Yamaoka Y. Prospective cohort study of transarterial chemoembolization for unresectable hepatocellular carcinoma in 8510 patients. Gastroenterology. 2006;131:461–9.
42. Bruix J, Sherman M. Management of hepatocellular carcinoma: an update. Hepatology. 2011;53:1020–2.
43. Llovet JM, Bruix J. Systematic review of randomized trials for unresectable hepatocellular carcinoma: chemoembolization improves survival. Hepatology. 2003;37:429–42.
44. Lo C-M, Ngan H, Tso W-K, Liu C-L, Lam C-M, Poon RT-P, Fan S-T, Wong J. Randomized controlled trial of transarterial lipiodol chemoembolization for unresectable hepatocellular carcinoma. Hepatology. 2002;35:1164–71.
45. Llovet JM, Real MI, Montaña X, Planas R, Coll S, Aponte J, Ayuso C, Sala M, Muchart J, Solà R, Rodés J, Bruix J. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. Lancet. 2002;359:1734–9.
46. Groupe d'Etude et de Traitement du Carcinome Hépatocellulaire. A comparison of lipiodol chemoembolization and conservative treatment for unresectable hepatocellular carcinoma. N Engl J Med. 1995;332:1256–61.
47. Yang HJ, Lee JH, Lee DH, et al. Small single-nodule hepatocellular carcinoma: comparison of transarterial chemoembolization, radiofrequency ablation, and hepatic resection by using inverse probability weighting. Radiology. 2014;271:909–18.
48. Kim HC. Role of C-arm cone-beam CT in chemoembolization for hepatocellular carcinoma. Korean J Radiol. 2015;16(1):114–24.
49. Varela M, Real MI, Burrel M, Forner A, Sala M, Brunet M, Ayuso C, Castells L, Montañá X, Llovet JM, Bruix J. Chemoembolization of hepatocellular carcinoma with drug eluting beads: efficacy and doxorubicin pharmacokinetics. J Hepatol. 2007;46:474–81.
50. Lammer J, Malagari K, Vogl T, Pilleul F, Denys A, Watkinson A, Pitton M, Sergent G, Pfammatter T, Terraz S, Benhamou Y, Avajon Y, Gruenberger T, Pomoni M, Langenberger H, Schuchmann M, Dumortier J, Mueller C, Chevallier P, Lencioni R. Prospective randomized study of doxorubicin-eluting-bead embolization in the treatment of

hepatocellular carcinoma: results of the PRECISION V study. Cardiovasc Intervent Radiol. 2010;33:41–52.
51. Gao S, Yang Z, Zheng Z, Yao J, Deng M, Xie H, Zheng S, Zhou L. Doxorubicin-eluting bead versus conventional TACE for unresectable hepatocellular carcinoma: a meta-analysis. Hepatogastroenterology. 2013;60(124):813–20.
52. Han S, Zhang X, Zou L, Lu C, Zhang J, Li J, Li M. Does drug-eluting bead transcatheter arterial chemoembolization improve the management of patients with hepatocellular carcinoma? A meta-analysis. PLoS One. 2014;9(8):e102686.
53. Laurent A, Wassef M, Chapot R, Houdart E, Merland J-J. Location of vessel occlusion of calibrated tris-acryl gelatin microspheres for tumor and arteriovenous malformation embolization. J Vasc Interv Radiol. 2004;15:491–6.
54. Dion JE, Rankin RN, Viñuela F, Fox AJ, Wallace AC, Mervart M. Dextran microsphere embolization: experimental and clinical experience with radiologic-pathologic correlation. Work in progress. Radiology. 1986;160:717–21.
55. Pillai KM, McKeever PE, Knutsen CA, Terrio PA, Prieskorn DM, Ensminger WD. Microscopic analysis of arterial microsphere distribution in rabbit liver and hepatic VX2 tumor. Sel Cancer Ther. 1991;7:39–48.
56. Yamamoto A, Imai S, Kobatake M, Yamashita T, Tamada T, Umetani K. Evaluation of tris-acryl gelatin microsphere embolization with monochromatic X rays: comparison with polyvinyl alcohol particles. J Vasc Interv Radiol. 2006;17:1797–802.
57. Bonomo G, Pedicini V, Monfardini L, Della Vigna P, Poretti D, Orgera G, Orsi F. Bland embolization in patients with unresectable hepatocellular carcinoma using precise, tightly size-calibrated, anti-inflammatory microparticles: first clinical experience and one-year follow-up. Cardiovasc Intervent Radiol. 2010;33:552–9.
58. Kluger MD, Halazun KJ, Barroso RT, Fox AN, Olsen SK, Madoff DC, Siegel AB, Weintraub JL, Sussman J, Brown RS Jr, Cherqui D, Emond JC. Bland embolization versus chemoembolization of hepatocellular carcinoma before transplantation. Liver Transpl. 2014;20(5):536–43.
59. Brown KT, Do RK, Gonen M, Covey AM, Getrajdman GI, Sofocleous CT, Jarnagin WR, D'Angelica MI, Allen PJ, Erinjeri JP, Brody LA, O'Neill GP, Johnson KN, Garcia AR, Beattie C, Zhao B, Solomon SB, Schwartz LH, DeMatteo R, Abou-Alfa GK. Randomized trial of hepatic artery embolization for hepatocellular carcinoma using doxorubicin-eluting microspheres compared with embolization with microspheres alone. J Clin Oncol. 2016;34(17):2046–53.

60. Salem R, Lewandowski RJ, Mulcahy MF, Riaz A, Ryu RK, Ibrahim S, Atassi B, Baker T, Gates V, Miller FH, Sato KT, Wang E, Gupta R, Benson AB, Newman SB, Omary RA, Abecassis M, Kulik L. Radioembolization for hepatocellular carcinoma using Yttrium-90 microspheres: a comprehensive report of long-term outcomes. Gastroenterology. 2010;138:52–64.
61. Kulik LM, Carr BI, Mulcahy MF, Lewandowski RJ, Atassi B, Ryu RK, Sato KT, Benson A, Nemcek AA, Gates VL, Abecassis M, Omary RA, Salem R. Safety and efficacy of 90Y radiotherapy for hepatocellular carcinoma with and without portal vein thrombosis. Hepatology. 2008;47:71–81.
62. Hilgard P, Hamami M, Fouly AE, Scherag A, Müller S, Ertle J, Heusner T, Cicinnati VR, Paul A, Bockisch A, Gerken G, Antoch G. Radioembolization with yttrium-90 glass microspheres in hepatocellular carcinoma: European experience on safety and long-term survival. Hepatology. 2010;52:1741–9.
63. Sangro B, Bilbao JI, Iñarrairaegui M, Rodriguez M, Garrastachu P, Martinez-Cuesta A. Treatment of hepatocellular carcinoma by radioembolization using 90Y microspheres. Dig Dis. 2009;27:164–9.
64. Ludwig JM, Zhang D, Xing M, Kim HS. Meta-analysis: adjusted indirect comparison of drug-eluting bead transarterial chemoembolization versus 90Y-radioembolization for hepatocellular carcinoma. Eur Radiol. 2017;27(5):2031–41.
65. Ku Y, Tominaga M, Iwasaki T, Fukumoto T, Muramatsu S, Kusunoki N, Sugimoto T, Suzuki Y, Kuroda Y, Saitoh Y. Efficacy of repeated percutaneous isolated liver chemoperfusion in local control of unresectable hepatocellular carcinoma. Hepatogastroenterology. 1998;45:1961–5.
66. Gerunda GE, Neri D, Merenda R, Barbazza F, Zangrandi F, Meduri F, Bisello M, Valmasoni M, Gangemi A, Faccioli AM. Role of transarterial chemoembolization before liver resection for hepatocarcinoma. Liver Transpl. 2000;6:619–26.
67. Graziadei IW, Sandmueller H, Waldenberger P, Koenigsrainer A, Nachbaur K, Jaschke W, Margreiter R, Vogel W. Chemoembolization followed by liver transplantation for hepatocellular carcinoma impedes tumor progression while on the waiting list and leads to excellent outcome. Liver Transpl. 2003;9:557–63.
68. Yao FY, Hirose R, LaBerge JM, Davern TJ, Bass NM, Kerlan RK, Merriman R, Feng S, Freise CE, Ascher NL, Roberts JP. A prospective study on downstaging of hepatocellular carcinoma prior to liver transplantation. Liver Transpl. 2005;11:1505–14.

69. Bharat A, Brown DB, Crippin JS, Gould JE, Lowell JA, Shenoy S, Desai NM, Chapman WC. Pre-liver transplantation locoregional adjuvant therapy for hepatocellular carcinoma as a strategy to improve longterm survival. J Am Coll Surg. 2006;203:411–20.
70. Obed A, Beham A, Püllmann K, Becker H, Schlitt HJ, Lorf T. Patients without hepatocellular carcinoma progression after transarterial chemoembolization benefit from liver transplantation. World J Gastroenterol. 2007;13:761–7.
71. Zangos S, Eichler K, Balzer JO, Straub R, Hammerstingl R, Herzog C, Lehnert T, Heller M, Thalhammer A, Mack MG, Vogl TJ. Large-sized hepatocellular carcinoma (HCC): a neoadjuvant treatment protocol with repetitive transarterial chemoembolization (TACE) before percutaneous MR-guided laser-induced thermotherapy (LITT). Eur Radiol. 2007;17:553–63.
72. Hoffmann K, Glimm H, Radeleff B, Richter G, Heining C, Schenkel I, Zahlten-Hinguranage A, Schirrmacher P, Schmidt J, Büchler MW, Jaeger D, Kalle C v, Schemmer P. Prospective, randomized, double-blind, multi-center, Phase III clinical study on transarterial chemoembolization (TACE) combined with Sorafenib versus TACE plus placebo in patients with hepatocellular cancer before liver transplantation—HeiLivCa [ISRCTN24081794]. BMC Cancer. 2008;8:349.
73. Zhou W-P, Lai ECH, Li A-J, Fu S-Y, Zhou J-P, Pan Z-Y, Lau WY, Wu M-C. A prospective, randomized, controlled trial of preoperative transarterial chemoembolization for resectable large hepatocellular carcinoma. Ann Surg. 2009;249:195–202.
74. Choi SB, Kim KS, Park YN, Choi JS, Lee WJ, Seong J, Han K-H, Lee JT. The efficacy of hepatic resection after neoadjuvant transarterial chemoembolization (TACE) and radiation therapy in hepatocellular carcinoma greater than 5 cm in size. J Korean Med Sci. 2009;24:242–7.
75. Schaudt A, Kriener S, Schwarz W, Wullstein C, Zangos S, Vogl T, Mehrabi A, Fonouni H, Bechstein WO, Golling M. Role of transarterial chemoembolization for hepatocellular carcinoma before liver transplantation with special consideration of tumor necrosis. Clin Transpl. 2009;23(Suppl 21):61–7.
76. Wang X, Li J, Peng Y, Dai Y, Xu W. Influence of preoperative transarterial chemoembolization on the prognosis for patients with resectable hepatocellular carcinoma: a meta-analysis of randomized trials. Hepatogastroenterology. 2011;58(107–108):869–74.
77. Yu T, Xu X, Chen B. TACE combined with liver resection versus liver resection alone in the treatment of resectable HCC: a meta-analysis. Chinese German J Clin Oncol. 2013;12:P532–6.

78. Si T, Chen Y, Ma D, Gong X, et al. Preoperative transarterial chemoembolization for resectable hepatocellular carcinoma in Asia area: a meta-analysis of random controlled trials. Scand J Gastroenterol. 2016;51(12):1512–9.
79. Lai EC, Lo CM, Fan ST, Liu CL, Wong J. Postoperative adjuvant chemotherapy after curative resection of hepatocellular carcinoma: a randomized controlled trial. Arch Surg. 1998;133:183–8.
80. Ono T, Yamanoi A, Nazmy El Assal O, Kohno H, Nagasue N. Adjuvant chemotherapy after resection of hepatocellular carcinoma causes deterioration of long-term prognosis in cirrhotic patients: metaanalysis of three randomized controlled trials. Cancer. 2001;91:2378–85.
81. Wen J, Shen W-L, Yang S-H. Adjuvant hepatic chemotherapy after resection of solitary hepatocellular carcinoma associated with hepatitis B virus cirrhosis. Hepatobiliary Pancreat Dis Int. 2006;5:224–7.
82. Li Q, Wang J, Sun Y, Cui YL, Juzi JT, Qian BY, Hao XS. Postoperative transhepatic arterial chemoembolization and portal vein chemotherapy for patients with hepatocellular carcinoma: a randomized study with 131 cases. Dig Surg. 2006;23:235–40.
83. Peng B-g, He Q, Li J-P, Zhou F. Adjuvant transcatheter arterial chemoembolization improves efficacy of hepatectomy for patients with hepatocellular carcinoma and portal vein tumor thrombus. Am J Surg. 2009;198:313–8.
84. Zhong J-H, Li L-Q. Postoperative adjuvant transarterial chemoembolization for participants with hepatocellular carcinoma: a meta-analysis. Hepatol Res. 2010;40:943–53.
85. Cheng X, Sun P, QG H, Song ZF, Xiong J, Zheng QC. Transarterial (chemo)embolization for curative resection of hepatocellular carcinoma: a systematic review and meta- analyses. J Cancer Res Clin Oncol. 2014;140:1159–70.
86. Furuse J, Ishii H, Satake M, Onaya H, Nose H, Mikami S, Sakai H, Mera K, Maru Y, Yoshino M. Pilot study of transcatheter arterial chemoembolization with degradable starch microspheres in patients with hepatocellular carcinoma. Am J Clin Oncol. 2003;26:159–64.
87. Huo T-I, Huang Y-H, Wu J-C, Chiang J-H, Lee P-C, Chang F-Y, Lee S-D. Sequential transarterial chemoembolization and percutaneous acetic acid injection therapy versus repeated percutaneous acetic acid injection for unresectable hepatocellular carcinoma: a prospective study. Ann Oncol. 2003;14:1648–53.
88. Dettmer A, Kirchhoff T-D, Gebel M, Zender L, Malek N-P, Panning B, Chavan A, Rosenthal H, Kubicka S, Krusche S, Merkesdal S, Galanski M, Manns M-P, Bleck J-S. Combination of repeated single-session percutaneous ethanol injection and transarterial chemoembolisation

compared to repeated single-session percutaneous ethanol injection in patients with non-resectable hepatocellular carcinoma. World J Gastroenterol. 2006;12:3707–15.
89. Kirchhoff TD, Bleck JS, Dettmer A, Chavan A, Rosenthal H, Merkesdal S, Frericks B, Zender L, Malek NP, Greten TF, Kubicka S, Manns MP, Galanski M. Transarterial chemoembolization using degradable starch microspheres and iodized oil in the treatment of advanced hepatocellular carcinoma: evaluation of tumor response, toxicity, and survival. Hepatobiliary Pancreat Dis Int. 2007;6:259–66.
90. Ishida K, Hirooka M, Hiraoka A, Kumagi T, Uehara T, Hiasa Y, Horiike N, Onji M. Treatment of hepatocellular carcinoma using arterial chemoembolization with degradable starch microspheres and continuous arterial infusion of 5-fluorouracil. Jpn J Clin Oncol. 2008;38:596–603.
91. Carr BI, Kondragunta V, Buch SC, Branch RA. Therapeutic equivalence in survival for hepatic arterial chemoembolization and yttrium 90 microsphere treatments in unresectable hepatocellular carcinoma: a two-cohort study. Cancer. 2010;116:1305–14.
92. Nagano H. Treatment of advanced hepatocellular carcinoma: intraarterial infusion chemotherapy combined with interferon. Oncology. 2010;78(Suppl 1):142–7.
93. Kucuk ON, Soydal C, Lacin S, Ozkan E, Bilgic S. Selective intraarterial radionuclide therapy with Yttrium-90 (Y-90) microspheres for unresectable primary and metastatic liver tumors. World J Surg Oncol. 2011;9:86.
94. Kondo M, Morimoto M, Numata K, Nozaki A, Tanaka K. Hepatic arterial infusion therapy with a fine powder formulation of cisplatin for advanced hepatocellular carcinoma with portal vein tumor thrombosis. Jpn J Clin Oncol. 2011;41:69–75.
95. Gao S, Zhang PJ, Guo JH, Chen H, HF X, et al. Chemoembolization alone vs combined chemoembolization and hepatic arterial infusion chemotherapy in inoperable hepatocellular carcinoma patients. World J Gastroenterol. 2015;21(36):10443–52.
96. Ibrahim SM, Kulik L, Baker T, Ryu RK, Mulcahy MF, Abecassis M, Salem R, Lewandowski RJ. Treating and downstaging hepatocellular carcinoma in the caudate lobe with yttrium-90 radioembolization. Cardiovasc Intervent Radiol. 2012;35:1094–101.
97. Zhang Y, Li Y, Ji H, Zhao X, Lu H. Transarterial Y90 radioembolization versus chemoembolization for patients with hepatocellular carcinoma: a meta-analysis. Biosci Trends. 2015;9(5):289–98.
98. Lobo L, Yakoub D, Picado O, Ripat C, Pendola F, et al. Unresectable hepatocellular carcinoma: radioembolization versus chemoembolization: a systematic review and meta-analysis. Cardiovasc Intervent Radiol. 2016;39(11):1580–8.