Review

Balloon-Occluded Transarterial Chemoembolization for Hepatocellular Carcinoma in the Modern Drug Therapy Era

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Reviews

Balloon-Occluded Transarterial Chemoembolization for Hepatocellular Carcinoma in the Modern Drug Therapy Era

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Simple Summary: Drug therapy for hepatocellular carcinoma is recommended in transarterial chemoembolization (TACE)-refractory and unsuitable cases. TACE has progressed in line with the progress in drug therapy. In Japan, TACE is broadly classified into conventional TACE, balloon occluded TACE, and drug-eluting beads TACE. However, the type of TACE recommended for TACE-refractory or unsuitable cases has not been elucidated, and a targeted approach for individual cases and appropriate TACE selection is important.

Abstract: The indications for TACE in the treatment of hepatocellular carcinoma have become more stringent with the development of systemic pharmacotherapy. Radical TACE is expected to be used only in situations such as for tumors with small volume which fulfill the "up-to-7". Furthermore, a combination of molecular-targeted agents is expected to maximize the efficacy of TACE. In the intermediate stage, TACE and drug therapy play complementary roles, and it is important to select a treatment strategy that considers tumor status and hepatic reserve. However, no studies have investigated the various types of TACE in the treatment of such patients. Currently, TACE in Japan is broadly classified into conventional TACE, balloon occluded TACE (B-TACE), and drug-eluting beads TACE (DEB-TACE). This article outlines the evolution of B-TACE for hepatocellular carcinoma in the drug therapy era.

Keywords: hepatocellular carcinoma; balloon occuluded transarterial chemoembolization; conventional transarterial chemoembolization; hemodynamic

1. Introduction

Hepatocellular carcinoma (HCC) accounts for >90% of primary liver tumors and is the leading cause of cancer death worldwide [1]. In cases of large tumor size or advanced HCC, hepatectomy is considered as the only curative treatment. However, even after radical hepatectomy, the recurrence rate for HCC is high, with postoperative recurrence in 50% and 80% of patients at 2 and 5 years, respectively [2,3]. Furthermore, intrahepatic recurrence is inevitable, even with local ablation [4,5]. There are two types of HCC recurrence: intrahepatic metastasis (IM), which is self-explanatory, and multicentric carcinogenesis (MC), in which a completely different clone of HCC arises due to a preexisting liver injury caused by the hepatitis virus or other factors. Intrahepatic recurrence accounts for >90% of the recurrent forms, and treatment is important for intrahepatic recurrent lesions.

To prevent recurrence, Togo et al. described the possibility of background liver treatment for prevention of MC and hepatic infusion for IM, with the use of both transarterial chemoembolization (TACE) and transarterial chemoinfusion (TAI) expected in the pharmacotherapy era [6].

In recent years, systemic drug therapy using molecular-targeted agents and immune checkpoint inhibitors has made remarkable progress, with proven efficacy and safety in managing HCC. The development of systemic drug therapy has changed the indications for conventional local therapy, with the indications for interventional radiology (IVR) becoming much stricter in particular. Here,

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we review the evolution of B-TACE, which has been performed mainly in Japan, and the role of IVR in the pharmacotherapy era.

2. What is TACE?

HCC epitomizes a hyper-vascularized tumor. Classic HCCs, such as intermediate-differentiated HCC and poorly differentiated HCC, have abundant arteries and are highly active in angiogenesis using vascular endothelial growth factor (VEGF) and other agents. These tumors cannot survive without a rich blood supply; therefore, in terms of treatment, interrupting the blood supply is of critical importance. TACE is a treatment that physically interrupts the blood supply, whereas molecularly targeted therapy using angiogenesis inhibitors (anti-VEGF inhibitors) is a treatment that chemically and pharmacologically interrupts the blood supply. Hepatic arterial chemoembolization is a treatment that combines both chemotherapy and embolization. An embolization material is injected through a catheter to physically occlude tumor blood vessels and induce a state of blood inhibition, resulting in cancer cell necrosis. In addition, a cytotoxic anticancer drug is injected directly into the tumor to ensure an effective concentration of the anticancer drug and to reduce the amount of the drug used. As such, the disadvantages of systemic administration have been overcome. However, since blood flow to normal hepatocytes is also reduced to some extent, the risk of impaired hepatic reserve remains the greatest challenge when using this therapy.

3. Changes in TACE indications

The indication for TACE is hyper-vascularized multiple HCC. The target is Barcelona Clinic Liver Cancer (BCLC-B): intermediate stage, which is the target recommended in international guidelines. The 2022 revision divides this intermediate stage into three groups: those meeting the extended Milan criteria; those in which tumor hyperstaining is clear, portal vein blood flow is maintained, and the tumor artery can be selected; and those that spread diffusely, infiltrate, or spread widely on both lobes. TACE is recommended for patients with clear tumor staining, portal vein blood flow, and where tumor artery selection is possible [7].

In 2014, microspheres (beads), which are spherical embolization materials, were approved in Japan for TACE, as opposed to conventional hepatic artery chemoembolization therapy (cTACE). TACE using drug-eluting beads (DEB-TACE) impregnated with anticancer drugs has also been accepted as a new therapeutic strategy. The notable feature of this method is the use of 100–500 μm microspherical embolization material instead of the 1–2 mm embolization materials used in cTACE. A micro balloon catheter was launched in Japan, with balloon occluded TACE (B-TACE) evolving accordingly [8].

4. B-TACE concepts

First, the hepatic artery is selectively occluded with a micro balloon catheter, and a lipiodol emulsion is injected while the arterial pressure is reduced. As a result, the arterial blood flow into the normal liver parenchyma stagnates early due to the viscosity of this solution and the pressure gradient between the arterial and portal veins becoming smaller.

However, tumor vessels have low vascular resistance and relatively preserved blood flow, limiting the influx of lipiodol into the normal liver parenchyma and relatively increasing lipiodol accumulation in the tumor.

Even when the hepatic artery is occluded, peripheral blood flow is maintained via anastomotic branches, peribiliary plexus, and isolated arteries. Therefore, a good occlusion effect is achieved when the balloon-occluded arterial stump pressure (BOASP) is <64 mmHg. A lower BOASP is considered likely to facilitate the injection of more lipiodol and embolic material into and around the tumor [8].

The balloon also prevents backflow of the anticancer drug and embolization material, which may reduce leakage outside the target node. In addition, the balloon allows a certain amount of pressure to be applied to the occluded distal area late in the infusion phase, which is considered to

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enhance the therapeutic effect by allowing lipiodol and embolization material to be pressurized into and around the tumor [9].

Balloon occlusion reduces the influx of lipiodol into the hepatic parenchyma, and is more advantageous than cTACE in terms of preserving hepatic function. B-TACE also has the advantage of reducing the number of vessel selections, even in tumors with multiple nutrient vessels, but the therapeutic effect is greatly influenced by the position of the balloon and the injection pressure of the lipiodol emulsion. In addition, less embolization material flows into the coronal staining zone, and the embolization area is expected to be wider.

Although the results and indications for B-TACE have not yet been clarified, B-TACE is expected to be effective in patients for whom there is difficulty in selectively inserting micro catheters or who have shown an inadequate response to cTACE.

Considering that B-TACE causes more vascular damage than cTACE, miriplatin, which causes less vascular damage, has been mainly used in Japan (Table 1). Compared with other anticancer drugs, miriplatin causes less vascular injury. B-TACE may cause hemodynamic changes that limit drug influx into the normal liver parenchyma and may lead to more concentrated drug accumulation in the tumor nodules due to the continuous influx of lipiodol emulsion into the tumor nodules. In some cases, the drug may be administered with miriplatin. In some cases, double platinum therapy using a combination of miriplatin and cisplatin has been used with good results [10].

Table 1. Summary of studies of therapeutic effect of miriplain-based balloon-occluded transarterial chemoembolization for hepatocellular carcinoma.

Ref.	Number of Patients	Clinical Background	Therapeutic Effect
Ishikawa et al. **[11]**	51	Mean laboratory values were as follows: AFP 233.66 ± 583.46 ng/mL, DCP 181.55 ± 335.09 mAU/mL, T-Bil 0.65 ± 0.27 mg/dL, albumin 3.64 ± 0.44 g/dL, prothrombin activity 91.12% ± 13.57% The mean Child-Pugh score was 6.37 ± 1.34.	The local recurrence rates at 6 and 12 months were 11.1% and 26.2%, respectively. The median recurrence time was 9 months.
Hatanaka et al. **[12]**	66	Child-Pugh Class A: 42, B :24, and C: 0 Number of tumors: one: 34, two: 10, three: 6, and four or more: 16 Maximum tumor diameter: 25.5 (range, 18–37) mm BCLC stage: Early stage 41/ Intermediate stage 25	CR 53.0%, PR 10.6%, SD 19.7%, PD 16.7%, RR, 63.6%
Minami et al. **[13]**	27	Countable HCC: 17; Uncountable HCC 10 Countable HCC:	Countable: TE4 43.8%, TE3 12.5%, TE2 37.5%, TE1 6.3%, RR, 56.3% Uncountable:

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		Child-Pugh class A: 11, B: 6, and C: 0 Tumor size, (mean ± SD) 2.0 ± 0.9 (range, 1.0–4.6) cm Uncountable HCC: Tumor size, (mean ± SD) approx. 1–2 cm	CR 0%, PR 0%, SD 10%, PD 90%
Kawamura et al. **[14]**	30	Child-Pugh Class A: 12, B: 18, and C: 0 Tumor diameter, 20 (range, 6–55) mm Tumor number per patient: one: 1, two: 9, three: 6, four: 4, and five or more: 5 1	TE4 51.0%, TE3 8.5%, TE2 19.1%, TE1 21.3%, RR, 59.6%
Asayama et al. **[15]**	29	Child–Pugh Class A: 25, B: 4, and C: 0	TE4 8.6%, TE3 48.6%, TE2 17.1%, TE1 25.7%, RR, 57.1%
Ogawa et al. **[16]**	33	Number of tumors: one: 13, two: 9, three: 5, four: 1, and five or more: 5 0 Stage I: 1, II: 10, III: 20, and Iva: 0 Child-Pugh Class A: 24, B: 7, and C: 2 Tumor size (initial treatment): 22 (range, 7-90) mm	TE4 49.2%
Arai et al. **[17]**	49	Child-Pugh class A: 36, B: 13, and C: 0 Stage I, 16, II: 33, and III: 0 Tumor size: 29 (range, 8–73) mm Portal vein invasion: none	TE4: 27, TE3: 19, TE2: 2, TE1: 1, RR: 93.9%

AFP, alpha-fetoprotein ; BCLC, Barcelona clinic liver cancer classification; CR, complete response; PR, partial response; SD, stable disease; PD, progress disease;; DCP, des-gamma-carboxyprothrombin; HCC, hepatocellular carcinoma,; TE,treatment effect.

B-TACE has been reported to have a better antitumor effect on target nodules compared with cTACE. Ishikawa et al. reported that the local recurrence rate of HCC treated with B-TACE was 11.1% at 6 months and 26.2% at 12 months, and the factor showing local recurrence was the computed tomography (CT) value immediately following B-TACE. Hatanaka et al. compared 49 patients treated with B-TACE and 48 patients treated with cTACE for single-agent HCC [12]. They reported that the B-TACE group received a significantly higher dose of miriplatin, and that the antitumor effect was significantly better in the B-TACE group. Furthermore, according to Ogawa et al., the percentage of treatment effect 4 (TE4) was significantly higher with B-TACE than that with cTACE, indicating a better antitumor effect.

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These reports consistently show that B-TACE allows more intratumoral injection of miriplatin and lipiodol, leading to a better therapeutic effect. Indeed, B-TACE has better antitumor efficacy in target nodules compared with cTACE. Factors that indicate treatment efficacy, including the appearance of new lesions as well as target nodules, are as follows: number of tumors (hazard ratio [HR] 4.44, 95% confidence interval [CI] 1.26–15.7, $p = 0.021$] and α-fetoprotein (AFP) (HR 11.40, 95% CI 2.75–46.9; $p = 0.001$). However, Minami et al. reported no benefit of B-TACE in uncountable multiple HCC, and this finding requires further investigation in future studies [13].

Kawamura et al. achieved TE4 in nodules with irregular ring enhancement and reported its usefulness for classically hyper-vascularized tumors [14]. Furthermore, anthracyclines have also been reported in B-TACE (Table 2), and post-embolization syndrome is frequently reported as an adverse effect (AE). In general, anthracyclines, including epirubicin, are considered to be highly damaging to the vasculature and should be administered with caution in B-TACE. There is also a risk of drug and embolic substances entering the vascular plexus around the bile ducts, which is not affected by using selective cTACE. Shirono et al. reported a higher rate of TE4 achievement with Epi-B-TACE compared with MPT-B-TACE [18], and Lucatteri et al. observed higher response rates at 1 month and at 3–6 months with complete response (CR) rates of 44.8% and 52.9%, respectively, and partial response (PR) rates of 55% and 23.5%, respectively [19].

Lucateri et al. reported no significant difference in AEs in comparison with DEB-TACE, although they found high antitumor effects in large HCCs treated with DEB-TACE [20].

B-TACE is safer than non-B-TACE methods such as cTACE and DEB-TACE, and it has a higher CR rate with a longer local recurrence-free period; given these, B-TACE is expected be to continuously used.

HCCs with a 30-50 mm diameter outperform cTACE [21], in propensity score matching (PSM) with cTACE, B-TACE has been found to be effective.

Concerning anthracycline B-TACE, the response rate is rising; however, the incidence of post-embolization syndrome and other AEs is higher than that in MPT-B-TACE, and safer treatment strategies are needed.

Table 2. Summary of studies of therapeutic effect of epirubicin-based balloon-occluded transarterial chemoembolization for hepatocellular carcinoma.

Ref.	Number of patients	Clinical background	Therapeutic effect
Shirono et al. **[18]**	30	PS 0: 24, PS 1: 6	The median LRF period obtained with B-TACE was 1180 days.
		Child–Pugh class A: 21, B: 9	The median LRF period after C-TACE was 389 days.
		Tumor size (mm): 21.0 (range, 11.3–65) mm	The median LRF period after DEB-TACE was 272 days.
		ALBI Grade 1: 9, 2: 21, 3: 0	There were significant differences among TACE procedures.
		BCLC stage 0: 1, A: 15, B: 7, C: 7	
		Number of tumor localized segments: >2 n = 11, ≤2 n = 19	
		Number of tumor nodules:	

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		≥4 n = 6, <3 n = 24	
Lucattelli et al. **[19]**	23	Type of malignancy: HCC 18, mCRC: 1, iCC: 2, sarcoma metastasis: 1, breast metastasis: 1 Mean maximum diameter: 4.4 cm (±1) Mean lesion volume: 31.4 cm3 (±14.4)	At 1 month HCC: CR 88.9%, PR 11.1%, RR 100.0% ICC: CR 100.0%, RR 100.0% Metastasis: CR 100.0%, RR 100.0% At 6 months HCC: CR 87.5%, PR 6.2%, PD 6.2%, RR 93.8% ICC: CR 100.0%, RR 100.0% Metastasis: CR 66.7.0%, PR 33.3%, RR 100.0%
Lucattelli et al. **[20]**	27	BCLC stage A: 10, B: 17 Median nodule diameter (mm): 27 mm (95% CI 23.0–35.1) Median number of nodules treated per patient: 1 (95% CI 1–2)	Contrast, signal-to-noise ratio, and contrast-to-noise ratio were all significantly higher in the b-DEB-TACE subgroup compared with the DEB-TACE subgroup (182.33 HU [95% CI 160.3-273.5] vs. 124 HU [95% CI 80.6-163.6]; 8.3 [95% CI 5.7-10.1] vs. 4.5 [95% CI 3.7-6.0]; 6.9 [95% CI 4.3-7.8] vs. 3.1 [95% CI 2.2-5.0] $p < 0.05$). Data
Golfieri et al. **[21]**	91	BCLC stage A: 50, B: 38, C: 3 Child-Pugh class at first TACE: A: 67, B: 24, C: 0	CR 59.3%, PR 30.8%, SD 5.5%, PD 4.4%, RR, 90.1%
Iezzi et al. **[22]**	5	Child–Pugh class A5: 3, A6: 2 HCC diameter: 5.7 ± 0.6 (range, 5.1–6.5) cm Location (hepatic segment):	CR 80.0%, PR 20.0%, RR 100.0%

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		V-VI: 1, VIII-V: 1, VI: 1 II-III 2	
Shirono et al. **[23]**	35	Child-Pugh Class A, 23; Class B, 12; Class C, 0 BCLC A, 15; BCLC B, 11; BCLC C, 9 Tumor size, 21 (range, 12.25–65) mm Number of tumor localized segments <2, n = 18; ≥3, n = 17 Number of tumor nodules ≤3, n = 21; <4, n = 14	Epirubicin (15.1 months) was significantly better than miriplatin (3.2 months) in prolonging the local TTP after B-TACE (p = 0.0293). Epirubicin showed a positive tendency in TE4 (100% tumor necrosis) rate when compared with miriplatin (p = 0.058).
Maruyama et al. [**24**]	50	Child–Pugh class A: 43, B: 7 Diameter of main target tumor: 3.2 ± 2.8 cm	No statistically significant difference was observed between the B-TACE and C-TACE groups

BCLC, Barcelona clinic liver cancer classification; CR, complete response; PR, partial response; SD, stable disease; PD, progress disease;, ; DCP, des-gamma-carboxyprothrombin; HCC, hepatocellular carcinoma ; iCC, intrahepatic cholangiocarcinoma; mCRC, metastatic colorectal cancer; PS, performance status; RR, response rate; TACE, transarterial chemoembolization; TE, treatment effect

Kim et al. reported that cisplatin-based B-TACE has also been used, and a high response rate was achieved even in cTACE-refractory, multiple, and BCLC-C patients [25]. and in PSM with cTACE, B-TACE has been found to be effective in HCCs >30 mm, with the target for treatment becoming clearer [26].

Table 3. Summary of studies of therapeutic effect of cisplatin-based balloon-occluded transarterial chemoembolization for hepatocellular carcinoma.

Ref.	Number of patients	Clinical background	Therapeutic effect
Kim et al. **[25]**	60	Child–Pugh score A: 51, B: 8, C: 1	CR 75.0%, PR 25.0%, RR 100.0%
		BCLC stage A: 31, B: 19, C: 10	median TTP was 5.3 months, median time to local recurrence was increased to 9.5 months
		Tumor number single 28, Multiple 32	progression-free survival rates were 56.8% and 9.2% at 6 and 12 months
Chu et al. **{26}**	32	ECOG PS 0: 31, PS1, 1	CR 93.8%, PR 6.2%, RR 100.0%

	Child–Pugh class A: 28, B: 4	CT HU of lipiodol accumulation (mean ± SD) 507.8 ±84.8
	Tumor size (cm, mean ± SD) 3.4 ± 1.2	Data

BCLC, Barcelona clinic liver cancer classification; CR, complete response; PR, partial response; SD, stable disease; PD, progress disease; HU, Hounsfeld units; ECOG, Eastern Cooperative Oncology Group performance status (ECOG PS) ; TTP, time to progression

5. Analyses of the hemodynamic usefulness of B-TACE

Sugimoto et al. reported that contrast-enhanced ultrasound can predict the accumulation of lipiodol emulsion and determine its therapeutic effect [27]. Kakuta et al. reported that the balloon occlusion at the third molecule enhances the stump pressure rather than the first branch [28]. Non-target B-TACE should not be performed based on stump pressure data. In addition, A1, A4, and A8 have an anastomosis and a communicating arcade, suggesting that B-TACE may be somewhat inefficient. However, there is a significant difference in the local recurrence rate depending on whether or not the CT value immediately after B-TACE is above average; it should be noted that it is necessary to obtain sufficient CT values to reduce local recurrence. While B-TACE is expected to be effective, it may not be possible to determine whether B-TACE is effective in all patients according to digital subtraction angiography alone. If the pixel value decreases under occlusion, B-TACE may not necessarily be effective. Therefore, it is important to measure the pixel values in accordance with cone-beam CT pre- and post-intraoperative balloon occlusion to differentiate between these cases [29,30]. In addition, Yoshimatsu et al. reported that the treatment effect was poor when the tumor occupied the central area and when computed tomographic hepatic angiopathy (CTHA) with balloon occlusion was insufficiently stained [31]. Asayama et al. reported that the treatment effect was poor when CTHA with balloon occlusion was performed with coronal staining, no coronal staining, or reduced perfusion defects compared with normal CTHA [15]. They also reported that CTHA with reduced perfusion defects was less effective than CTHA without coronal staining, CTHA with coronal staining, or CTHA with normal staining.

6. Conclusion

We reviewed the evolution of B-TACE use in the era of pharmacotherapy and its current indications. TACE has previously predominated in the intermediate stage; however, with the development of pharmacotherapy, the indications for TACE have narrowed. This issue is not whether TACE or drug therapy is better, but rather that there needs to be consideration of each indication to maximize therapeutic efficacy and minimize deterioration of the hepatic reserve. Furthermore, it is important to consider the synergistic combination of these therapies to maximize the therapeutic effect. In the era of pharmacotherapy, B-TACE may play a complementary role.

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Informed Consent Statement: Written informed consent was obtained from all patients before treatment and this study received ethical approval for use of an opt-out methodology based on low risk to the participants.

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References

1. Sung, H.; Ferlay, J.; Siegel, R.L.; Laversanne M.; Soerjomataram I.; Jemal A.; Bray F. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2021, 71, 209–249.
2. Taura, K.; Ikai, I.; Hatano, E.; Fujii H.; Uyama N.; Shimahara Y. Implication of frequent local ablation therapy for irltrahepatic recurrence in prolonged survival of patients with hepatocellular carcinoma undergoing hepatic resection : an analysis of 610 patients over 16 years old. *Ann Surg* ***2006***, 244, 265−273.
3. Imamura, H.; Matsuyama, Y.; Tanaka, E.; Ohkubo, T.; Hasegawa, K.; Miyagawa, S.; Sugawara, Y.; Minagawa, M.; Takayama, T.; Kawasaki, S.; Makuuchi, M. Risk factors contributing to early and late phase intrahepatic recurrence of hepatocellular carcinoma after hepatectomy. *J Hepatol* **2003,** 38, 200-207.
4. Shiina, S.; Tateishi, R.; Arano, T.; Uchino, K.; Enooku, K.; Nakagawa, H.; Asaoka, Y.; Sato, T.; Masuzaki, R.; Kondo, Y.; Goto, T.; Yoshida, H.; Omata, M.; Koike, K. Radiofrequency ablation for hepatocellular carcinoma: 10-year outcome and prognostic factors. *Am J Gastroenterol* **2012**, 107, 569-77.
5. Ishikawa, T.; Michitaka, I.; Kamimura, H.; Higuchi, K.; Kubota, T.; Seki, K.; Ohta, H.; Yoshida, T.; Kamimura, T. Oral branched-chain amino acids administration improves impaired liver dysfunction after radiofrequency ablation therapy for hepatocellular carcinoma. *Hepatogastroenterology* **2009**, 56, 1491-1495.
6. Togo, S.; Tanaka, K.; Masui, H.; Matsuo, K.; Morioka, D.; Kurosawa, H.; Miura, Y.; Endo, I.; Sekido, H.; Shimada, H. Usefulness of prophylactic transcatheter arterial infusion of anticancer agents with lipiodol to prevent recurrence of hepatocellular carcinoma after hepatic resection. *Int Surg* **2005,** 90, 103-108.
7. Reig, M.; Forner, A.; Rimola, J. ; Ferrer-Fàbrega J, Burrel M, Garcia-Criado Á, Kelley RK, Galle PR, Mazzaferro V, Salem R, Sangro B, Singal AG, Vogel A, Fuster J, Ayuso C, Bruix J. BCLC strategy for prognosis prediction and treatment recommendation : The 2022 update. *J Hepatol* **2022,** 76, 681-693.
8. Irie, T.; Kuramochi, M.; Takahashi, N. Dense accumulation of lipiodol emulsion in hepatocellular carcinoma nodule during selective balloon-occluded transarterial chemoembolization: measurement of balloon-occluded arterial stump pressure. *Cardiovasc Intervent Radiol* **2013**, 36, 706-13.
9. Hatanaka, T.; Arai, H.; Kakizaki, S. Balloon-occluded transcatheter arterial chemoembolization for hepatocellular carcinoma. *World J Hepatol* **2018**, 10, 485-495.
10. Ishikawa, T.; Abe, S.; Watanabe, T.; Nozawa, Y.; Sano, T.; Iwanaga, A.; Seki, K.; Honma, T.; Yoshida, T. Improved survival with double platinum therapy transcatheter arterial infusion using cisplatin and transcatheter arterial chemoembolization using miriplatin for BCLC-B hepatocellular carcinoma. *Mol Clin Oncol* **2016**, 5, 511-516.
11. Ishikawa, T.; Abe, S.; Inoue, R.; Sugano, T.; Watanabe, Y.; Iwanaga, A.; Seki, K.; Honma, T.; Nemoto, T.; Takeda, K.; Yoshida, T. Predictive factor of local recurrence after balloon-occluded TACE with miriplatin (MPT) in hepatocellular carcinoma. *PLoS One* **2014**, 9, e103009, doi:10.1371/journal.pone.
12. Hatanaka, T.; Arai, H.; Shibasaki, M.; Tojima, H.; Takizawa, D.; Toyoda, M.; Takayama, H.; Abe, T.; Sato, K.; Kakizaki, S.; Yamada, M. Factors predicting overall response and overall survival in hepatocellular carcinoma patients undergoing balloon-occluded transcatheter arterial chemoembolization: A retrospective cohort study. *Hepatol Res* **2018,** 48, 165-175.
13. Minami, Y.; Minami, T.; Chishina, H.; Arizumi, T.; Takita, M.; Kitai, S.; Yada, N.; Hagiwara, S.; Tsurusaki, M.; Yagyu, Y.; Ueshima, K.; Nishida, N.; Murakami, T.; Kudo, M. Balloon-occluded transcatheter arterial chemoembolization for hepatocellular carcinoma: a single-center experience. *Oncology* **2015**, 89, 27-32.
14. Kawamura, Y.; Ikeda, K.; Fujiyama, S.; Hosaka, T.; Kobayashi, M.; Saitoh, S.; Sezaki, H.; Akuta, N.; Suzuki, F.; Suzuki, Y.; Arase, Y.; Kumada, H. Usefulness and limitations of balloon-occluded transcatheter arterial chemoembolization using miriplatin for patients with four or fewer hepatocellular carcinoma nodules. *Hepatol Res* **2017**, 47, 338-346.

15. Asayama, Y.; Nishie, A.; Ishigami, K.; Ushijima, Y.; Takayama, Y.; Okamoto, D.; Fujita, N.; Morita, K.; Honda, H. Hemodynamic changes under balloon occlusion of hepatic artery: predictor of the short-term therapeutic effect of balloon-occluded transcatheter arterial chemolipiodolization using miriplatin for hepatocellular carcinoma. *Springerplus* **2016**, 5, 157, doi:10.1186/s40064-016-1880-7.
16. Ogawa, M.; Takayasu, K.; Hirayama, M.; Miura, T.; Shiozawa K.; Abe, M.; Matsumoto, N.; Nakagawara, H.; Ohshiro, S.; Yamamoto, T.; Tanaka, N.; Moriyama, M.; Mutou, H.; Yamamoto, Y.; Irie, T. Efficacy of a microballoon catheter in transarterial chemoembolization of hepatocellular carcinoma using miriplatin, a lipophilic anticancer drug: Short-term results. *Hepatol Res* **2016**, 46, E60-9.
17. Arai, H.; Abe, T.; Takayama, H.; Toyoda, M.; Ueno, T.; Kakizaki, S.; Sato, K. Safety and efficacy of balloon-occluded transcatheter arterial chemoembolization using miriplatin for hepatocellular carcinoma. *Hepatol Res* **2015**, 45, 663-666.
18. Shirono, T.; Iwamoto, H.; Niizeki, T.; Shimose, S.; Nakano, M.; Satani, M.; Okamura, S.; Noda, Y.; Kamachi, N.; Kuromatsu, R.; Sakai, M.; Nomiyama, M.; Kuwano, T.; Tanaka, M.; Koga, H.; Torimura, T. Epirubicin is more effective than miriplatin in balloon-occluded transcatheter arterial chemoembolization for hepatocellular carcinoma. *Oncology* **2019**, 96, 79-86.
19. Lucatelli, P.; Ginnani Corradini, L.; De Rubeis, G.; Rocco, B.; Basilico, F.; Cannavale, A.; Nardis, P.G.; Corona, M.; Saba, L.; Catalano, C.; Bezzi, M. Balloon-occluded transcatheter arterial chemoembolization (b-TACE) for hepatocellular carcinoma performed with polyethylene-glycol epirubicin-loaded drug-eluting embolics: safety and preliminary results. *Cardiovasc Intervent Radiol* **2019**, 42, 853-862.
20. Lucatelli, P.; De Rubeis, G.; Rocco, B.; Basilico, F.; Cannavale, A.; Abbatecola, A.; Nardis, P.G.; Corona, M.; Brozzetti, S.; Catalano, C.; Bezzi, M. Correction to: Balloon occluded TACE (B-TACE) vs DEM-TACE for HCC: a single center retrospective case control study. *BMC Gastroenterol* **2021**, 21, 282, doi:10.1186/s12876-021-01861-y.
21. Golfieri, R.; Bezzi, M.; Verset, G.; Fucilli, F.; Mosconi, C.; Cappelli, A.; Paccapelo, A.; Lucatelli, P.; Magand, N.; Rode, A.; De Baere, T. Balloon-occluded transarterial chemoembolization: in which size range does it perform best? a comparison of its efficacy versus conventional transarterial chemoembolization, using propensity score matching. *Liver Cancer* **2021,** 10, 522-534.
22. Iezzi, R.; Posa, A.; Tanzilli, A.; Carchesio, F.; Pompili, M.; Manfredi, R. Balloon-occluded MWA (b-MWA) followed by balloon-occluded TACE (b-TACE): technical note on a new combined single-step therapy for single large HCC. *Cardiovasc Intervent Radiol* **2020** , 43, 1702-1707, doi:10.1007/s00270-020-02583-6.
23. Shirono, T.; Iwamoto, H.; Niizeki, T.; Shimose, S.; Kajiwara, A.; Suzuki, H.; Kamachi, N.; Noda, Y.; Okamura, S.; Nakano, M.; Kuromatsu, R.; Murotani, K.; Koga, H.; Torimura, T. Durable complete response is achieved by balloon-occluded transcatheter arterial chemoembolization for hepatocellular carcinoma. *Hepatol Commun* **2022**, 6, 2594-2604.
24. Maruyama, M.; Yoshizako, T.; Nakamura, T.; Nakamura, M.; Yoshida, R.; Kitagaki, H. Initial experience with balloon-occluded trans-catheter arterial chemoembolization (B-TACE) for hepatocellular carcinoma. *Cardiovasc Intervent Radiol* **2016**, 39, 359-66.
25. Kim, P.H.; Gwon, D.I.; Kim, J.W.; Chu, H.H.; Kim, J.H. The safety and efficacy of balloon-occluded transcatheter arterial chemoembolization for hepatocellular carcinoma refractory to conventional transcatheter arterial chemoembolization. *Eur Radiol* **2020**, 30, 5650-5662.
26. Chu, H.H.; Gwon, D.I.; Kim, G.H.; Kim, J.H.; Ko, G.Y.; Shin, J.H.; Ko, H.K.; Yoon, H.K. Balloon-occluded transarterial chemoembolization versus conventional transarterial chemoembolization for the treatment of single hepatocellular carcinoma: a propensity score matching analysis. *Eur Radiol* **2023**, 33, 2655-2664.
27. Sugimoto, K.; Saguchi, T.; Saito, K.; Imai, Y.; Moriyasu, F. Hemodynamic changes during balloon-occluded transarterial chemoembolization (B-TACE) of hepatocellular carcinoma observed by contrast-enhanced ultrasound. *J Med Ultrason* **2014,** 41, 209-15, doi:10.1007/s10396-013-0487-7.
28. Kakuta, A; Shibutani, K.; Ono, S.; Miura, H.; Tsushima, F.; Kakehata, S.; Basaki, K.; Fujita, H.; Seino, H.; Fujita, T.; Takai, Y. Temporal variations in stump pressure and assessment of images obtained from cone-beam computed tomography during balloon-occluded transarterial chemoembolization. *Hepatol Res* **2016,** 46, 468-76.
29. Ishikawa, T.; Abe, S.; Hoshii, A.; Yamada, Y.; Iiduka, A.; Nemoto, T.; Takeda, K.; Yoshida, T. Cone-Beam Computed Tomography Correlates with Conventional Helical Computed Tomography in Evaluation of Lipiodol Accumulation in HCC after Chemoembolization. *PloS One* **2016**, 11, e0145546, doi:10.1371/journal.pone.0145546.

30. Ishikawa, T.; Imai, M.; Owaki, T.; Sato, H.; Nozawa, Y.; Sano, T.; Iwanaga, A.; Seki, K.; Honma, T.; Yoshida, T.; Kudo, M. Hemodynamic changes on cone-beam computed tomography during balloon-occluded transcatheter arterial chemoembolization using miriplatin for hepatocellular carcinoma: a preliminary study. *Dig Dis* **2017**, 35, 598-601.
31. Yoshimatsu, R.; Yamagami, T.; Ishikawa, M.; Kajiwara K.; Aikata H.; Chayama K.; Awai K. Change in Imaging Findings on Angiography-Assisted CT During Balloon-Occluded Transcatheter Arterial Chemoembolization for Hepatocellular Carcinoma. *Cardiovasc Intervent Radiol* **2016**, 39, 865-74.