Transcatheter arterial chemoembolization followed by surgical resection for hepatocellular carcinoma: a focus on its controversies and screening of patients most likely to benefit

Zhan-Qi Wei[1], Yue-Wei Zhang[2]

[1]School of Medicine, Tsinghua University, Haidian District, Beijing 100084, China;
[2]Beijing Tsinghua Changgung Hospital, School of Clinical Medicine, Tsinghua University, Beijing 102218, China.

Abstract

Surgical resection (SR) is recommended as a radical procedure in the treatment of hepatocellular carcinoma (HCC). However, postoperative recurrence negatively affects the long-term efficacy of SR, and preoperative adjuvant therapy has therefore become a research hotspot. Some clinicians adopt transcatheter arterial chemoembolization (TACE) as a preoperative adjuvant therapy in patients undergoing SR to increase the resection rate, reduce tumor recurrence, and improve the prognosis. However, the findings of the most relevant studies remain controversial. Some studies have confirmed that preoperative TACE cannot improve the long-term survival rate of patients with HCC and might even negatively affect the resection rate. Which factors influence the efficacy of preoperative TACE combined with SR is a topic worthy of investigation. In this review, existing clinical studies were analyzed with a particular focus on several topics: screening of the subgroups of patients most likely to benefit from preoperative TACE, exploration of the optimal treatment regimen of preoperative TACE, and determination of the extent of tumor necrosis as the deciding prognostic factor.

Keywords: Hepatocellular carcinoma; Surgical resection; Transcatheter arterial chemoembolization; Adjuvant therapy

Introduction

Hepatocellular carcinoma (HCC) is the third most common cancer worldwide, and its mortality rate has been increasing.[1] In several treatment guidelines, surgical resection (SR) is recommended as a radical procedure for HCC. Unfortunately, the practical effectiveness of SR is not ideal. Some clinicians adopt transcatheter arterial chemoembolization (TACE) as a preoperative adjuvant therapy to improve the prognosis in patients undergoing SR. However, the results of the most relevant studies remain controversial, and no consensus has been reached regarding the influence of preoperative TACE on the prognosis of patients with HCC. Determining the indications for preoperative TACE and improving its therapeutic effectiveness are still problems that need to be solved. In an effort to develop an internationally validated technical recommendation for the standardization of preoperative TACE, this review was performed to analyze existing observational studies and randomized controlled trials with a particular focus on several topics regarding preoperative TACE before SR: screening of the subgroups of patients with HCC most likely to benefit from preoperative TACE, exploration of the optimal treatment regimen of preoperative TACE, and determination of the predictors of therapeutic effectiveness.

HCC combination therapy with TACE and SR

HCC is suitable for locoregional treatment. HCC tends to stay within the liver until it reaches an advanced stage, with distant metastasis generally occurring in the late stages.[2] This suggests that an effective locoregional treatment has a great impact on the course of HCC. Furthermore, the hepatic artery becomes the only feeding vessel of most (90%–100%) HCC tumors. Therefore, when the hepatic artery is used as a pathway to treat HCC, organs, and tissues other than the liver are less severely affected.[3] TACE can be used as an adjuvant treatment of HCC by making rational use of the above-mentioned characteristics of HCC.

Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.1097/CM9.0000000000001767

Correspondence to: Yue-Wei Zhang, Beijing Tsinghua Changgung Hospital, School of Clinical Medicine, Tsinghua University, 168 Litang Road, Changping District, Beijing 102218, China
E-Mail: zhangyuewei1121@sina.com

Chinese Medical Journal 2021;134(19)
Received: 07-05-2021 **Edited by:** Ning-Ning Wang

TACE

TACE is a selective chemotherapy method that delivers chemotherapy drugs via an artery, allowing the drugs to function directly upon the tumor. Lipiodol serves as the embolization agent and is mixed and delivered within the same process.[4] Because of the selective deposition of lipiodol within tumors and the good control of tumor growth by chemotherapy drugs, the blood supply to the tumor will be reduced, tumor necrosis will be promoted, and malignant changes of residual liver tumor tissue will be avoided.[5]

TACE is an attractive option because it can be administered regardless of the size, location, and the number of tumors.[6] With the recent advances in interventional radiology, TACE is now widely used as a palliative treatment for unresectable HCC.[7-11] TACE has also become one of the most widely used postoperative adjuvant treatments after SR.[12-15] In recent years, TACE has been used as a preoperative treatment before liver transplantation and SR.[16,17]

Improvement of prognosis by preoperative TACE

The main purpose of preoperative TACE is to inactivate HCC cells and shrink the tumor by embolizing the feeding artery of the tumor. Xiao *et al*[18] reported that preoperative TACE may enhance apoptosis of HCC cells by upregulating the expression of Bax protein and downregulating the expression of Bcl-2 protein and the ratio of Bcl-2 to Bax protein expression. Therefore, preoperative TACE can contribute to tumor shrinkage, thus achieving the following three results. First, the unresectable HCC is transformed into resectable HCC, expanding the surgical indications for SR. Second, the R0 resection rate improves and the possibility of postoperative recurrence decreases. Third, the residual liver volume significantly increases, leading to a significant improvement in 5-year survival.[19-22] Furthermore, TACE has advantages in destroying small tumors and treating satellite nodules; thus, it can help to eliminate microtumor lesions that cannot be excised by SR.[23]

TACE is also performed to inhibit the dissemination of HCC cells during surgical operations, thus reducing tumor recurrence. This has been demonstrated by measuring the levels of messenger RNA of albumin or alpha-fetoprotein in hepatic or peripheral veins.[24] Lu *et al*[25] reported that preoperative TACE enhances expression of the metastasis suppressors nm23-H1 and TIMP-2 and may inhibit metastasis of HCC. Moreover, in some cases, TACE was confirmed to not only promote the formation of the capsule but also increase the thickness of the capsule. An intact capsule has been demonstrated to be associated with a low rate of tumor metastasis.[16]

Because lipiodol can maintain dense deposition in tumors, some microtumor lesions in the liver that were not found in the early stage can be found by digital subtraction angiography during the TACE procedure and by a plain computed tomography scan of the liver 1 month after SR.[19] TACE can detect tumors with a diameter of 2 mm and even tiny satellite nodules.[26] Therefore, TACE helps clinicians to avoid incomplete removal of nodules during SR and thus reduce the risk of early recurrence.

Ren *et al*[27] reported that microparticle-TACE (mTACE) could significantly reduce the proportion of regulatory T (Treg) cells in the peripheral blood of patients with HCC. This indicates that mTACE has a positive regulatory effect on the anticancer immune function of patients with HCC.

Detrimental effects of preoperative TACE

Notably, some clinicians indicated that preoperative TACE has detrimental effects. Marukuchi *et al*[17] reported that preoperative TACE was a significant predictor of deterioration of the remnant liver function in their univariate analysis ($P = 0.0230$). TACE itself often causes many adverse reactions. In addition to the abnormalities associated with the postembolization syndrome, such as transient fever, abdominal pain, nausea, vomiting, and elevated transaminases, severe adverse events, such as ascites, deterioration of liver function, tumor progression or metastasis before the operation, bacteremia, and bleeding from the femoral puncture site have also been occasionally observed.[28] Arslan and Degirmencioglu[29] suggested that a treated tumor measuring >5 cm, treatment of more than one tumor, and failure to perform the procedure in a superselective fashion increase the risk of postembolization syndrome after TACE.

Some main arguments against preoperative TACE are complications, such as perihepatic adhesions, which make SR more difficult; the increased risk of liver damage and liver failure; the delay of SR, which turns some resectable tumors into unresectable tumors; the increased difficulty of future TACE because of enhanced collateral feeding artery formation for recurrent tumors; and reduced stability of residual tumor cells, which makes these cells more likely to metastasize into the blood during SR.

In addition, some studies have shown that TACE is a risk factor for contrast-induced nephropathy in patients with HCC.[15,30] Nishihara *et al*[31] reported that some post-therapeutic patients with HCC might develop HCC with a biliary phenotype, indicating more aggressive malignancies. Therefore, whether preoperative TACE can inhibit tumor recurrence and prolong survival in patients with HCC undergoing SR remains controversial.

Considering the detrimental effects of TACE from the viewpoint of the underlying mechanism, preoperative TACE has been reported to enhance angiogenesis of HCC cells by upregulating the protein expression of vascular endothelial growth factor (VEGF), and serial measurement of the VEGF level 1 day before and 7 days after TACE may be used to predict rapid HCC growth.[18,32] Sergio *et al*[33] further found that when TACE is not totally effective, it might induce a significant neoangiogenetic reaction and affect patient survival as suggested by an increase in VEGF and basic fibroblast growth factor following treatment. Shim *et al*[34] and Xuan *et al*,[35] respectively, demonstrated that a marked increase in the serum VEGF level 1 to 2 days after TACE in patients with HCC was associated with distant metastasis and unfavorable outcomes. Wang and Li[36] proved that inhibition of the Wnt/β-catenin signaling pathway reduces the expression of VEGF and improves the therapeutic effect of TACE by suppressing migration and

invasion and promoting apoptosis of transplanted HCC cells in rats. Furthermore, Zhao *et al*[37] reported that CXCR7-shRNA inhibited tumor invasion and metastasis to improve the efficacy of TACE in patients with HCC by reducing the expressions of CXCR7, matrix metalloproteinase 2, and VEGF. Zhou *et al*[38] reported that treatment with zoledronic acid significantly inhibited the secretion of VEGF and enhanced the effects of TACE by inhibiting tumor-associated macrophage infiltration and tumor angiogenesis in rat models of HCC. Wu *et al*[39] demonstrated that arterial infusion of rapamycin combined with TACE could improve treatment efficacy by decreasing hypoxia-inducible factor 1α (HIF-1α), VEGF, inducible nitric oxide synthase, and CD34 expression. Lin *et al*[40] reported that suppressing the interleukin 8/HIF-1α/phosphoinositide 3-kinase pathway and mitogen-activated protein kinase/extracellular signal-regulated kinase pathway after TACE in patients with HCC might inhibit hypoxia-induced angiogenesis.

In addition, Kajihara *et al*[41] reported that preoperative TACE upregulated the expression of mesenchymal–epithelial transition factor (c-Met) in HCC and that this upregulated c-Met expression might be responsible for TACE refractoriness. It has been proven that the hepatocyte growth factor and its high-affinity receptor, c-Met, are closely related to the onset, progression, and metastasis of multiple tumors. The hepatocyte growth factor/c-Met axis is involved in cell proliferation, movement, differentiation, invasion, angiogenesis, and apoptosis by activating multiple downstream signaling pathways.[42]

Screening of subgroups of patients who benefit from preoperative TACE

TACE is widely accepted as one of the most effective therapeutic modalities for unresectable HCC. In recent years, TACE has also been used as a preoperative adjuvant treatment in patients with resectable HCC. As mentioned above, TACE has outstanding advantages as well as non-negligible disadvantages. Thus, several studies have focused on whether preoperative TACE is beneficial in patients with resectable HCC. However, the conflicting conclusions among different studies might be due to the limitations of these studies.[28] Sciarra *et al*[43] found that up to 60% of patients with HCC who underwent TACE did not benefit from the treatment despite multiple sessions. In addition, a subsequent meta-analysis largely did not support a survival benefit of routine preoperative TACE for all patients undergoing SR of HCC[16,44-52] [Table 1]. These findings suggest that TACE might have a positive effect on certain subgroups of patients with resectable HCC. Thus, patient selection is essential for effective and safe TACE. However, predicting which patients with HCC will respond to TACE has proven to be extremely difficult.[53]

Patients with advanced HCC

Sasaki *et al*[54] found that preoperative TACE significantly reduced the 5-year overall survival rate in patients with stage I or II tumors. However, Sugo *et al*[55] reported that in patients with stage III or IV tumors, preoperative TACE could significantly reduce the number and scope of recurrent tumors, thereby improving the pattern of tumor recurrence (i.e., reducing the incidence of extrahepatic metastasis and diffuse intrahepatic metastasis). Similar results have been reported elsewhere. Zhong *et al*[12] reported that preoperative TACE can improve the prognosis of patients with stage IIIA HCC. Moreover, for patients undergoing mesohepatectomy, the long-term prognosis of patients treated with preoperative TACE was also significantly improved.[56] These findings suggest that TACE is a safe and effective preoperative adjuvant treatment for patients with advanced HCC and that TACE should be avoided in patients with early HCC.

Patients with large tumors

Randomized controlled trials and observational studies have shown that almost all beneficial results of TACE occurred in patients with relatively large tumors (≥5 or 8 cm).[22,57] Notably, these studies showing that patients with resectable HCC did not benefit from preoperative TACE were conducted on patients with tumors of <5 cm[3,12,24,45,47,48,58-62] [Table 2]. In addition, Terasawa *et al*[57] reported that TACE before portal vein embolization increases the degree of hypertrophy of the future remnant liver after portal vein embolization and yields improved oncologic outcomes in patients with large HCCs planning to undergo major hepatectomy. This means that only when the average diameter of the tumor is >5 cm does TACE have potential value for SR of HCC. Therefore, the present findings suggest that clinicians should avoid performing preoperative TACE in patients with small HCCs. Based on these data, Morshid *et al*[53] reported that quantitative imaging features obtained prior to therapy can improve the accuracy of predicting the response of HCC to TACE. This approach is likely to provide useful information for aiding patient selection for TACE.

There are two explanations for the favorable effect of preoperative TACE on large tumors. First, in general, the proportion of microvascular invasion of large HCC is relatively high. Some studies have shown that postoperative TACE can effectively reduce the aggressiveness of microvascular invasion, thereby reducing recurrence.[63-65] Yang *et al*[52] reported that preoperative TACE may achieve a similar effect on patients. Furthermore, Wang *et al*[66] strongly recommended preoperative TACE in patients with HCC exhibiting microvascular invasion and reported that preoperative TACE could benefit patients with "middle risk" according to the current staging systems. Second, R0 resection is difficult to achieve for large HCC, especially massive HCC. Surgery becomes easier and the R0 resection rate improves after TACE has induced tumor necrosis and shrinkage.[67]

Avoidance of preoperative TACE in patients with poor liver function

Because HCC is often accompanied by chronic liver disease, such as chronic hepatitis or cirrhosis, the liver

Table 1: Results of TACE plus SR *vs.* SR alone for all patients with hepatocellular carcinoma.

Reference	Year	Inclusion period	Country	No. of patients		1/3/5-year DFS (%)			1/3/5-year OS (%)		
				TACE+SR	SR	TACE+SR	SR	*P*	TACE+SR	SR	*P*
Harada et al[44]	1996	1982–1994	Japan	98	33	69.7/37.6/30.2	68.8/33.7/28.8	NS	90.9/77.9/53.2	96.9/67.8/46.4	NS
Lu *et al*[45]	1996	1987–1993	China	26	51	61.5/51.4/39.2*	60.8/45.9/36.4*	>0.05	88.5/62.9/44.0	82.3/50.6/18.6	>0.05
Majno *et al*[46]	1997	1985–1995	France	49	27	63/33/29	63/22/11	0.043	NR	NR	NR
Lu *et al*[47]	1999	1988–1994	China/Japan	44	76	80/30/20	80/40/20	0.72	90/55/37	90/55/30	0.75
Choi *et al*[48]	2007	1998–2005	Korea	117	152	76.0/57.7/53.1	70.9/53.8/46.8	0.516	NR	NR	NR
Kim *et al*[49]	2008	1995–2000	Korea	97	237	60/46/NR	70/49/NR	0.011	75/NR/44	89/NR/62	0.67
Kang *et al*[50]	2010	1997–2007	Korea	32	64	58/36/7	77/58/32	0.01	78/60/26	97/83/45	0.11
Nishikawa *et al*[16]	2013	2004–2012	Japan	110	125	73.3/48.9/33.2	73.3/29.4/16.3	0.062	87.4/76.0/62.5	94.9/79.0/57.8	0.674
Lei *et al*[51]	2014	2005–2008	China	183	405	76.0/55.7/43.7	79.5/61.7/49.6	0.205	80.9/65.0/54.1	83.7/68.9/57.5	0.739
Yang *et al*[52]	2021	2010–2014	China	590	1034	80.33/55.21/39.41	78.24/58.34/47.90	0.032	93.89/72.82/62.23	94.48/80.81/68.62	0.027

* 1-/2-/3-year disease-free survival (%). DFS: disease-free survival; NS: not significant; NR: not reported; OS: overall survival; SR: surgical resection; TACE: transcatheter arterial chemoembolization.

Table 2: Results of TACE plus SR *vs.* SR alone for subgroups of patients with certain sizes of hepatocellular carcinoma.

Reference	Year	Inclusion period	Country	Tumor size (cm)	No. of patients		1/3/5-year DFS (%)			1/3/5-year OS (%)		
					TACE+SR	SR	TACE+SR	SR	*p*	TACE+SR	SR	*p*
Yamasaki *et al*[58]	1996	1987–1989	Japan	2–5	50	47	NR/NR/39.1	NR/NR/31.1	NS	NR/NR/62.7	NR/NR/61.7	NS
Lu *et al*[45]	1996	1987–1993	China	3–8	14	33	50.0/33.3/16.6*	72.7/54.2/39.7*	>0.05	85.7/31.2/0	84.8/58.7/27.9	>0.05
				>8	12	18	75.0/56.2/45.0*	38.9/32.4/10.8*	<0.05	91.6/82.5/53.0	77.8/30.1/0	<0.05
Lu *et al*[47]	1999	1988–1994	China/Japan	2–8	24	57	66/34/21*	78/57/43*	0.18	87/42/35	91/61/37	0.21
				>8	20	19	80/55/32*	50/22/11*	0.06	90/53/42	72/33/11	0.01
Ren *et al*[59]	2004	1995–1998	China	≤5	77	174	NR	NR		93.48/75.85/62.39	97.39/70.37/50.85	0.3956
				>5	108	190	NR	NR		89.67/61.28/44.36	69.95/49.86/37.40	0.0216
Choi *et al*[48]	2007	1998–2005	Korea	≤3	30	59	80/55/55	80/65/55	0.95	NR	NR	
				3–5	46	44	80/57/42	75/50/40	0.9	NR	NR	
				>5	44	50	75/55/55	60/42/37	0.146	NR	NR	
Zhou *et al*[3]	2009	2001–2003	China	≥5	52	56	48.9/25.5/12.8	39.2/21.4/8.9	0.372	73.1/40.4/30.7	69.6/32.1/21.1	0.679
Zhong *et al*[12]	2009	2001–2004	China	>5	57	58	29.7/9.3/9.3	14.0/3.5/1.7	0.04	80.7/33.3/23.0	56.5/19.4/17.5	0.048
Yamishita *et al*[24]	2012	1995–2008	Japan	≥5	42	95	NR/NR/43	NR/NR/37	0.04	NR/NR/57	NR/NR/43	0.02
Ha *et al*[60]	2016	2002–2011	Korea	2–5	105	830	29.9/57.2/62.8/68.8†	18.3/41.2/51.4/63.4†	0.005	97.1/80.0/70.4/60.4	97.7/90.3/83.4/69.6	0.003
Amisaki *et al*[61]	2016	2004–2012	Japan	2–5	34	87	68.7/44.9/44.9	90.8/62.6/49.4	0.043	87.5/62.3/62.3	97/93.9/80.5	0.014
Li *et al*[62]	2019	2004–2014	China	≥10	88	289	53.6/32.1/21.6	35.7/17.7/13.7	0.016	78.6/46.2/35.3	58.3/34.5/24.5	0.035

* 1-/2-/3-year disease-free survival (%). † 1-/3-/5-/10-year tumor recurrence rate (%). DFS: disease-free survival; NS: not significant; NR: not reported; OS: overall survival; SR: surgical resection; TACE: transcatheter arterial chemoembolization.

function of some patients with HCC is abnormal.[54] Several studies have investigated the importance of maintaining liver function for survival and have considered that poorer liver function is associated with worse clinical outcomes.[68] Treatment with branched-chain amino acids to maintain liver function has been shown to optimize clinical outcomes.[16] In addition, the histopathological examination has shown that preoperative TACE might lead to inflammatory injury of liver tissue, further deterioration of liver function, and even liver failure.[3] Thus, severe impairment of liver function is generally considered a contraindication to preoperative TACE.[3] These findings indicate that neoadjuvant preoperative TACE, such as TACE with drug-eluting beads (which is helpful to reduce the damage to liver function), is worthy of further clinical study.

As one of the most common genetic changes in HCC, TP53 mutation is associated with worse survival in patients with HCC.[69] Xue *et al*[70] reported that vascular invasion and TP53 mutation were significantly correlated with TACE failure/refractoriness in patients with hepatitis B virus (HBV)-related advanced HCC. They also found that mitogen-activated protein kinase and apoptosis pathways induced by TP53 mutation were possibly associated with TACE failure/refractoriness.[70] Furthermore, Wang and Bi[71] proved that patients with HCC who carry the AC + CC genotype of pri-let-7a-2 rs629367 after TACE had a worse prognosis than those who carry the AA genotype. These findings suggest that the efficacy of TACE may also be related to mutations in oncogenes. The relationship between the efficacy of TACE and oncogenes deserves further study. Moreover, one study showed that tumors with TP53 mutations had less CD8+ T-cell infiltration and more Foxp3+ Treg cell infiltration than those without TP53 mutations.[72] This suggests that the efficacy of TACE might be related to the tumor immune microenvironment, and it reminds clinicians to paid attention to studies focusing on the effect of TACE on the tumor immune response.

Exploration of optimal treatment regimen of preoperative TACE

The diversity of effectiveness of TACE may be associated with the number of TACE sessions performed and the interval between TACE and SR.[18,55] In many cohort studies, however, the TACE procedure is not guaranteed to be the same for every patient; thus, the conclusions of such studies may not be sufficiently accurate or objective. Moreover, the treatment regimens of preoperative TACE vary from study to study. This may be part of the reason why different studies draw conflicting conclusions. Presently, most clinicians still mainly rely on their own experience and the actual clinical situation to determine the treatment regimen of TACE, which cannot guarantee that preoperative TACE is beneficial for every patient with HCC.

Number of TACE sessions

Kim *et al*[73] proposed that the best response could not always be achieved after one session of TACE, especially for large tumors. Georgiades *et al*[74] reported that half of the patients who did not respond to initial TACE ultimately achieved a response and that improved clinical outcomes were observed after a second course. Therefore, Zhang *et al*[19] recommended that at least two more TACE sessions should be performed before SR regardless of tumor size. However, Paye *et al*[75] suggested that the recurrence rate of HCC also increases with additional TACE sessions. Choi *et al*[48] reported that repeated TACE did not increase the incidence of complete tumor necrosis. Furthermore, Yu *et al*[76] reported that repeated TACE resulted in tight adhesion of the tumor to the diaphragm and thickening of the hepatoduodenal ligament. Chen *et al*[56] pointed out that the inconvenience caused by TACE in surgical manipulation could be alleviated by not more than two TACE sessions. In addition, Kim *et al*[77] suggested that the optimal number of TACE sessions in an individual patient is unpredictable. However, they found that the effectiveness of initial TACE is a robust predictor of a favorable outcome.[77] Therefore, no uniform conclusion about the optimal number of TACE sessions can be drawn from the current studies.

Interval between preoperative TACE and SR

The effects of the interval between preoperative TACE and SR should be considered from three aspects: the safety of SR, including the difficulty and delay of the operation; the effectiveness of TACE; and the possibility of tumor recurrence.

First, Nagasue *et al*[78] suggested that if the interval between the last TACE and SR is long enough, such as 130 days, the intraoperative bleeding volume in patients with HCC undergoing preoperative TACE is similar to that in patients not undergoing preoperative TACE. Another potential drawback of preoperative TACE is the delay of surgery. In some cases, patients failed to undergo SR in time because of disease progression, extrahepatic metastasis, or liver failure.[3] Second, the effectiveness of TACE depends on the duration of the interaction among the embolic agent, chemotherapy drug, and tumor. If the interval is 1 to 2 months, TACE may be ineffective. If the interval is several months, TACE can inhibit the growth of the tumor and keep the tumor at an early stage.[5] However, it has been reported that excessively long intervals between the last TACE session and SR may lead to cancer cell growth and the invasion of new blood vessels, increasing the likelihood of HCC recurrence.[79] Therefore, clinicians should comprehensively consider the safety of SR, including the difficulty and delay of the operation; the effectiveness of TACE; and the possibility of tumor recurrence, ideally finding a balance among these three factors to optimize the treatment effect of preoperative TACE. However, the optimal treatment time cannot be determined solely based on clinicians' experience. We hope that big data technology can be introduced in the future to assist clinicians in establishing the most reasonable treatment plan. In addition, clinicians will determine the exact time point of SR according to the tumor diameter, degree of embolization, the recovery rate of liver function, and comprehensive preoperative evaluation results, including the indocyanine green retention rate at 15 min and future liver remnant volume.

Extent of tumor necrosis as the deciding prognostic factor

Differences in the tumor size and stage, TACE treatment regimen, Child–Pugh grade, and interventional radiologist's experience may result in potential heterogeneity of TACE effectiveness, and these factors have also been deemed outcome predictors.[28,80] However, different studies often arrive at conflicting conclusions about the effects of these factors. Although this might be due to the limitations of these studies, it has also been suggested that these factors might not directly affect the outcome. Si *et al*[81] and Kishore *et al*[82] reported that the degree of pathological necrosis is a predictor of recurrence-free survival and overall survival in post-resection and transplant patients.

Deposition of lipiodol determines the extent of tumor necrosis

A significant linear correlation has been reported between tumor necrosis and lipiodol uptake.[83] Zhang *et al*[19] further indicated that tumor necrosis was mainly due to long-term (>20-day) deposition of lipiodol. Sieghart *et al*[84] suggested that subtotal tumor necrosis (>90%) was associated with the absence of residual enhancement and diffuse accumulation of lipiodol throughout the nodule. Nishikawa *et al*[16] found that the effectiveness of TACE could be predicted by the degree of lipiodol deposition in the lesions as shown by computed tomography 2 weeks to 1 month after the first TACE session and that the degree of tumor necrosis and the state of capsule formation could be demonstrated by magnetic resonance imaging about 2 months after TACE. Therefore, the deposition of lipiodol can be used to judge the extent of tumor necrosis and thus predict the effectiveness of TACE.

Complete tumor necrosis improves prognosis

Patients with HCC undergoing preoperative TACE who develop complete tumor necrosis reportedly have better disease-free survival than those who do not respond to TACE.[54] Of course, part of the reason for this outcome may be that a completely necrotic tumor itself is more likely to have favorable tumor-related factors, such as a smaller tumor size and more complete tumor capsular.[85] However, there is increasing evidence that complete tumor necrosis improves the prognosis[46,48,49] (Table 3). In addition, Ochiai *et al*[86] proposed that the direct effects of TACE on patients, such as complete tumor necrosis, do not directly improve the outcome by themselves; other factors also contribute to this process. However, complete tumor necrosis, whether through direct or indirect effects, can be seen as a predictive marker of TACE improving the outcome of SR. Therefore, a TACE procedure to maximize the necrotic effect for the entire tumor area might be preferable in clinical practice, provided that liver function permits.[77]

Incomplete tumor necrosis increases the risk of tumor recurrence

A pathological incomplete response of the tumor has been reported to increase the risk of tumor recurrence.[60] The

Table 3: Comparison of patients with hepatocellular carcinoma: complete tumor necrosis *vs.* incomplete tumor necrosis *vs.* without preoperative TACE.

Reference	Year	Inclusion period	Country	No. of patients			1/3/5-year DFS (%)				1/3/5-year OS (%)			
				CN	IN	no-TACE	CN	IN	no-TACE	*P*	CN	IN	no-TACE	*P*
Majno *et al*[46]	1997	1985–1995	France	24	25	27	63/37/22	63/19/11	63/21/13	0.16			NR	
Choi *et al*[48]	2007	1998-2005	Korea	33	84	152	87.9/67.2/40.3	71.4/53.6/53.6	70.9/53.9/46.8	0.149*/0.165†			NR	
Kim *et al*[49]	2008	1995–2000	Korea	52	45	237	75/60/50	40/30/30	75/50/40	0.003	90/75/55	60/40/35	90/75/55	<0.001

*P for CN *vs.* non-TACE. †*P* value for CN *vs.* IN. CN: complete tumor necrosis; DFS: disease-free survival; IN: incomplete tumor necrosis; NR: not reported; OS: overall survival; SR; surgical resection; TACE: transcatheter arterial chemoembolization.

survival rate of patients with incomplete tumor necrosis is lower than that of patients with complete necrosis or without preoperative TACE[46,48,49] (Table 3). Furthermore, Liou *et al*[87] reported that incomplete tumor necrosis after TACE was related to the occurrence of lung metastasis.

Based on current studies, the mechanism can be explained as follows. First, necrosis weakens the adhesion ability of tumor cells. In cases of partial tumor necrosis, the remaining tumor cells are more likely to be moved into the bloodstream during surgical manipulation, thus increasing the risk of postoperative recurrence.[16,19,50,60,83,88] Wu *et al*[89] reported that the number of circulating tumor cells in the nonresponse group was significantly higher than the pretreatment level. Li *et al*[5] pointed out that the establishment of collateral circulation after TACE may lead to more vulnerable growth in other parts of the tumor with high metastatic potential. Second, ischemic necrosis caused by preoperative TACE has been reported to promote compensatory proliferation and increase the proliferative activity of non-embolized tumor cells.[90] This view has also been confirmed by the discovery that a high proliferating cell nuclear antigen labeling index was significantly more frequent in patients undergoing preoperative TACE.[91] Third, TACE induces tumor angiogenesis. Several studies have shown that VEGF, HIF-1α, and Dickkopf-related protein 1 were significantly elevated in the peripheral blood of patients with HCC undergoing TACE when tumor necrosis was incomplete.[33,34,89,92,93] In addition, residual liver tumor cells might develop resistance to chemotherapy drugs and became more difficult to treat than tumors not treated with TACE.[5]

Factors affecting the extent of tumor necrosis

Allard *et al*[6] reported that no patients with tumor necrosis of ≤90% attained a survival benefit, suggesting that only complete or near-complete tumor necrosis induced by preoperative TACE is a reliable predictor of a good prognosis. However, complete necrosis is uncommon; its rate ranges from 0% to 50% but is generally only around 20%.[48,55] Notably, although the effectiveness of TACE varies from patient to patient, clinicians should still follow a certain pattern in its implementation. Theoretically, the baseline tumor burden (including the tumor size and number), the tumor biology (including tolerance to ischemic stress and sensitivity to chemotherapeutic agents), the TACE treatment regimen (including the number of TACE procedures and the time interval between TACE and SR), and the patient's procedure-related physical condition (including vascular accessibility for intervention and deterioration of liver function during multiple TACE sessions) play important roles in determining the overall success rates of TACE procedures.[77,94,95] This also means that most of these factors may affect the extent of tumor necrosis. Therefore, clinicians should identify the patients most likely to benefit from preoperative TACE based on these factors and establish a reasonable TACE treatment regimen for each patient according to the individual situation. The extent of tumor necrosis should also be considered as an important reference for the next treatment.

Several issues that deserve further study

By combining a review of the literature with our clinical experience, we have identified some interesting but underappreciated issues related to TACE.

Interference with efficacy of TACE by antiviral therapy

Systemic chemotherapy leads to immune suppression and possible reactivation of HBV, suggesting the need for antiviral therapy in patients with HBV-related HCC.[96] TACE is not a systemic chemotherapy, but a high incidence of HBV reactivation was reported to be induced by TACE in patients with HBV-related HCC.[97] Peng *et al*[98] reported that TACE might increase the risk of HBV reactivation in HBsAg-negative/anti-HBc-positive patients diagnosed with unresectable HCC. Wang *et al*[99] reported that HBV DNA-negative patients with HCC still had a risk of HBV reactivation after TACE. Wang *et al*[100] reported that HBV reactivation after TACE is an independent prognostic factor and a crucial reason for a poor prognosis and lower survival rate of patients with HCC. However, Xu *et al*[96] reported that TACE could decrease the HBV DNA level in patients with HCC. Park *et al*[101] suggested that TACE did not aggravate HBV hepatitis in patients with HBV-related HCC. We still believe that TACE can induce HBV reactivation because this mainstream view is supported by more solid laboratory and clinical evidence. In addition, Liu *et al*[102] revealed that HBV-related HCC is less sensitive to TACE treatment than non-HBV-associated HCC. These findings indirectly prove the need for antiviral therapy and immune enhancers to improve the curative effect and prognosis of patients with HCC.

Antiviral therapy can reduce the risk of reactivation, helping to improve liver function after TACE.[99] Gao *et al*[103] reported that interferon therapy after TACE resulted in few adverse effects, low recurrence, and long survival in patients with HBV-related HCC. Zeng *et al*[104] suggested that 125I seed implantation combined with chemotherapy and antiviral therapy could effectively eliminate HBV DNA, improve liver function, increase the quality of life, and enhance the therapeutic effect in patients with HBV-related HCC. Ikeda *et al*[105] and Kubo *et al*,[106] respectively, reported that interferon-α and interferon-β decreased the recurrence of hepatitis C virus (HCV)-related HCC. Zuo *et al*[107] reported that the 3- and 5-year overall survival rates were significantly higher and that the recurrence rate was significantly lower in the TACE/interferon-α group than in the TACE group. In addition, Lin *et al*[108] reported that patients with decreased pre-TACE white blood cell counts have a potential risk of reactivation of HBV or HCV replication after TACE.

Given that many cases of HCC develop from hepatitis caused by viral infection (especially in China), and considering that the treatment regimen in most previous clinical studies did not involve combination with antiviral therapy (especially those studies in the 1990s), the postoperative antiviral therapy that has become standard and widely used in recent years appears to have played a critical role in HCC treatment. In the absence of antiviral

therapy, the effect of TACE on inhibition of tumor recurrence is masked by the fact that the virus is very likely to promote tumor recurrence after surgery. Therefore, we suggest that clinicians should implement strict antiviral therapy in addition to TACE to improve the prognosis for patients with HCC. In addition, the mechanism of HBV activation by TACE should be further studied to optimize the treatment and improve the technology of TACE.

Interestingly, the conclusions of studies from the Asia-Pacific region and those of studies from other areas have often been contradictory. HBV infection is dominant in patients with HCC in the Asia-Pacific region, whereas HCV infection or alcoholic cirrhosis is predominant in patients in other regions, especially in Europe and the United States. Based on the aforementioned role of TACE in activating the virus, TACE might have different effects on HCC caused by different etiologies, which may lead to different outcomes when combined with SR.

Efficacy of mTACE is superior to that of conventional TACE by improving immunity

In recent years, some clinicians have attempted to treat HCC with mTACE. This procedure involves the use of microembolic agents, such as gelatin sponge microparticles (GSMs) and biocompatible polymer poly(D,L-lactide-co-glycolide) (PLGA) microparticles, used alone or in combination with chemotherapeutic agents during TACE. These clinicians reported that the efficacy of mTACE in patients with HCC is better than that of conventional TACE.[109-111]

There are three explanations for the better efficacy of mTACE. First, it is well known that deposits of lipiodol in the liver can damage normal tissue, reduce liver reserve function, and potentially cause serious adverse effects. However, for patients with Child–Pugh B stage HCC, life expectancy may be dominated by the liver dysfunction rather than by the tumor progression itself. Therefore, the choice of TACE is critical because TACE itself can become a dangerous tool that is likely to precipitate liver dysfunction to an extent that survival is shortened rather than prolonged. The microparticles used in mTACE degrade within 7 to 14 days after embolization is achieved, which greatly reduces the detrimental effects on normal liver tissue.[112] Hence, mTACE may contribute to surgical safety. Chiang *et al*[113] reported that biodegradable microspheres have the advantage of enabling local embolization therapy with reduced adverse effects. Minici *et al*[114] demonstrated that degradable starch microsphere-TACE had an excellent safety profile, maintaining an efficacy that guarantees a clear advantage on the dropout rate, thus justifying its use.

Second, a unified and standardized microparticle size has not yet been established in clinical practice. Variable diameter microparticles are used in mTACE, including 150 to 350 μm, 350 to 560 μm, 560 to 710 μm, and 710 to 1000 μm. Microparticles with different diameters can selectively embolize tumor-supplying arteries with diameters close to theirs, and the embolization effect is significantly better than that of lipiodol. Therefore, mTACE is considered to cause more extensive tumor necrosis than conventional TACE, which can more rapidly reduce the tumor load because of the combined microsphere sizing strategy. In addition, Kamran *et al*[115] and Liu *et al*[110] used 350- to 560-μm GSMs as the embolic agent and verified that GSM-TACE is a safe and effective method for patients with the Barcelona Clinic Liver Cancer stage B HCC.

Third, Ren *et al*[27] reported that the proportion of Treg cells at 1 to 2 weeks postoperatively was significantly lower than that before mTACE. According to our clinical experience, mTACE may be able to more fully expose tumor antigens than conventional TACE, thereby triggering a more intense antitumor immune response. The advantage of mTACE in releasing tumor antigens is suspected to be due to more complete tumor necrosis, but no solid evidence is yet available.

However, although mTACE has the above benefits, the research on mTACE is lacking and the clinical use of mTACE is not adequately widespread. Combination therapy with mTACE and SR requires further investigation. We believe that as the technology advances, TACE will be used with more effective and safer embolization agents. This will require bold exploration by clinicians.

Conclusion

In this review, existing clinical studies were analyzed in an attempt to determine the factors influencing the efficacy of preoperative TACE combined with SR. Based on the collected data, we have drawn the following conclusions. First, only when the average diameter of the tumor is >5 cm, does TACE have potential value for SR of HCC; thus, clinicians should avoid administering preoperative TACE to patients with small HCCs. Second, although no uniform conclusion about the optimal number of TACE sessions can be drawn from the current studies, there is ample evidence that the interval between preoperative TACE and SR should be determined by the clinician with consideration of the patient's actual situation. Third, the extent of tumor necrosis induced by TACE is the deciding factor that truly determines the prognosis of patients with HCC. More complete tumor necrosis is associated with a better prognosis. How to improve the long-term curative effect of SR for HCC has been a hotspot issue in clinical research during the past 20 years. Preoperative TACE combined with SR continues to generate debate. How to more accurately screen patients who are most likely to benefit from preoperative TACE may become the next research focus. In addition, TACE treatment methods and models have been constantly updated and improved. The safety and efficacy of preoperative TACE combined with SR for HCC may also be a new research topic.

Funding

This work was supported by a grant from (1) the National Natural Science Foundation of China (No. 81571783); (2) Capital's Funds for Health Improvement and Research (2020-2-2242).

Conflicts of interest

None.

References

1. Ikeda K. Recent advances in medical management of hepatocellular carcinoma. Hepatol Res 2019;49:14–32. doi: 10.1111/hepr.13259.
2. Lau WY, Yu SCH, Lai ECH, Leung TWT. Transarterial chemoembolization for hepatocellular carcinoma. J Am Coll Surg 2006;202:155–168. doi: 10.1016/j.jamcollsurg.2005.06.263.
3. Zhou WP, Lai ECH, Li AJ, Fu SY, Zhou JP, Pan ZY, *et al*. A prospective, randomized, controlled trial of preoperative transarterial chemoembolization for resectable large hepatocellular carcinoma. Ann Surg 2009;249:195–202. doi: 10.1097/SLA.0b013e3181961c16.
4. Yamashita Y, Taketomi A, Itoh S, Harimoto N, Morita K, Fukuhara T, *et al*. Phase I/II study of the lipiodolization using DDP-H (CDDP powder; IA-call (A (®))) in patients with unresectable hepatocellular carcinoma. Cancer Chemother Pharmacol 2010;65:301–307. doi: 10.1007/s00280-009-1034-5.
5. Li HL, Ji WB, Zhao R, Duan WD, Chen YW, Wang XQ, *et al*. Poor prognosis for hepatocellular carcinoma with transarterial chemoembolization pre-transplantation: Retrospective analysis. World J Gastroenterol 2015;21:3599–3606. doi: 10.3748/wjg.v21.i12.3599.
6. Allard MA, Sebagh M, Ruiz A, Guettier C, Paule B, Vibert E, *et al*. Does pathological response after transarterial chemoembolization for hepatocellular carcinoma in cirrhotic patients with cirrhosis predict outcome after liver resection or transplantation? J Hepatol 2015;63:83–92. doi: 10.1016/j.jhep.2015.01.023.
7. Lo CM, Ngan H, Tso WK, Liu CL, Lam CM, Poon RTP, *et al*. Randomized controlled trial of transarterial lipiodol chemoembolization for unresectable hepatocellular carcinoma. Hepatology 2002;35:1164–1171. doi: 10.1053/jhep.2002.33156.
8. Nouso K, Wakuta A, Kariyama K. Combination therapy of transcatheter arterial chemoembolization with axitinib for the treatment of inoperable hepatocellular carcinoma. Ann Transl Med 2020;8:1039. doi: 10.21037/atm.2020.03.198.
9. Zhao J, Wu J, He M, Cao M, Lei J, Luo H, *et al*. Comparison of transcatheter arterial chemoembolization combined with radiofrequency ablation or microwave ablation for the treatment of unresectable hepatocellular carcinoma: a systemic review and meta-analysis. Int J Hyperthermia 2020;37:624–633. doi: 10.1080/02656736.2020.1774667.
10. Wang Z, Zhang H, Zhao H, Wang X, Tsauo J, Luo X, *et al*. Repeated transcatheter arterial chemoembolization is safe for hepatocellular carcinoma in cirrhotic patients with transjugular intrahepatic portosystemic shunt. Diagn Interv Radio 2014;20:487–491. doi: 10.5152/dir.2014.13493.
11. Liu L, Yu Y, Zhang C, Luo X, Tsauo J, Tang C, *et al*. Hepatobiliary and pancreatic: hepatocellular carcinoma supplied by portal blood after repeated transcatheter arterial chemoembolization. J Gastroenterol Hepatol 2012;27:1408. doi: 10.1111/j.1440-1746.2012.07170.x.
12. Zhong C, Guo RP, Li JQ, Shi M, Wei W, Chen MS, *et al*. A randomized controlled trial of hepatectomy with adjuvant transcatheter arterial chemoembolization versus hepatectomy alone for stage III A hepatocellular carcinoma. J Cancer Res Clin Oncol 2009;135:1437–1445. doi: 10.1007/s00432-009-0588-2.
13. Liang L, Li C, Diao Y-K, Jia H-D, Xing H, Pawlik TM, *et al*. Survival benefits from adjuvant transcatheter arterial chemoembolization in patients undergoing liver resection for hepatocellular carcinoma: a systematic review and meta-analysis. Therap Adv Gastroenterol 2020;13:1–14. doi: 10.1177/1756284820977693.
14. Huo YR, Chan MV, Chan C. Resection plus post-operative adjuvant transcatheter arterial chemoembolization (TACE) compared with resection alone for hepatocellular carcinoma: a systematic review and meta-analysis. Cardiovasc Intervent Radiol 2020;43:572–586. doi: 10.1007/s00270-019-02392-6.
15. Hayashi M, Abe K, Fujita M, Okai K, Takahashi A, Ohira H. Acute kidney injury after platinum-based transcatheter arterial chemoembolization and transarterial infusion chemotherapy in patients with hepatocellular carcinoma. Jpn J Clin Oncol 2020;50:36–43. doi: 10.1093/jjco/hyz129.
16. Nishikawa H, Arimoto A, Wakasa T, Kita R, Kimura T, Osaki Y. Effect of transcatheter arterial chemoembolization prior to surgical resection for hepatocellular carcinoma. Int J Oncol 2013;42:151–160. doi: 10.3892/ijo.2012.1711.
17. Marukuchi R, Furukawa K, Iwase R, Yasuda J, Shiozaki H, Onda S, *et al*. Risk factors for deterioration of remnant liver function after hepatic resection for hepatocellular carcinoma. Anticancer Res 2019;39:5755–5760. doi: 10.21873/anticanres.13777.
18. Xiao EH, Li DT, Shen SB, Zhou SK, Tan LH, Wang YH, *et al*. Effect of preoperative transcatheter arterial chemoembolization on apoptosis of hepatocellular carcinoma cells. Chin Med J 2003;116:203–207. doi: 10.1136/gut.52.suppl_2.ii31.
19. Zhang ZJ, Liu Q, He J, Yang JM, Yang GS, Wu MC. The effect of preoperative transcatheter hepatic arterial chemoembolization on disease-free survival after hepatectomy for hepatocellular carcinoma. Cancer 2000;89:2606–2612. doi: 10.1002/1097-0142(20001215)89:12<2606::AID-CNCR13>3.0.CO;2-T.
20. Kaibori M, Tanigawa N, Kariya S, Ikeda H, Nakahashi Y, Hirohara J, *et al*. A prospective randomized controlled trial of preoperative whole-liver chemolipiodolization for hepatocellular carcinoma. Dig Dis Sci 2012;57:1404–1412. doi: 10.1007/s10620-012.
21. Aoki T, Imamura H, Hasegawa K, Matsukura A, Sano K, Sugawara Y, *et al*. Sequential preoperative arterial and portal venous embolizations in patients with hepatocellular carcinoma. Arch Surg 2004;139:766–774. doi: 10.1001/archsurg.139.7.766.
22. Zhang CW, Dou CW, Zhang XL, Liu XQ, Huang DS, Hu ZM, *et al*. Simultaneous transcatheter arterial chemoembolization and portal vein embolization for patients with large hepatocellular carcinoma before major hepatectomy. World J Gastroenterol 2020;26:4489–4500. doi: 10.3748/wjg.v26.i30.4489.
23. Gao ZH, Bai DS, Jiang GQ, Jin SJ. Review of preoperative transarterial chemoembolization for resectable hepatocellular carcinoma. World J Hepatol 2015;7:40–43. doi: 10.4254/wjh.v7.i1.40.
24. Yamashita Y, Takeishi K, Tsuijita E, Yoshiya S, Morita K, Kayashima H, *et al*. Beneficial effects of preoperative lipiodolization for resectable large hepatocellular carcinoma (> = 5 cm in diameter). J Surg Oncol 2012;106:498–503. doi: 10.1002/jso.23098.
25. Lu W, Li YH, He XF, Mo YY, Zhu ZY. Transcatheter arterial chemoembolization enhances expression of Nm23-H1 and TIMP-2 in the tumor tissue of patients with hepatocellular carcinoma. Hepatogastroenterology 2011;58:558–564.
26. Yumoto Y, Jinno K, Tokuyama K, Araki Y, Ishimitsu T, Maeda H, *et al*. Hepatocellular carcinoma detected by iodized oil. Radiology 1985;154:19–24. doi: 10.1148/radiology.154.1.2981112.
27. Ren Z, Yue Y, Zhang Y, Dong J, Liu Y, Yang X, *et al*. Changes in the peripheral blood Treg cell proportion in hepatocellular carcinoma patients after transarterial chemoembolization with microparticles. Front Immunol 2021;12:624789. doi: 10.3389/fimmu.2021.624789.
28. Cheng X, Sun P, Hu QG, 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;140:1159–1170. doi: 10.1007/s00432-014-1677-4.
29. Arslan M, Degirmencioglu S. Risk factors for postembolization syndrome after transcatheter arterial chemoembolization. Curr Med Imaging Rev 2019;15:380–385. doi: 10.2174/1573405615666181122145330.
30. Aoe M, Kanemitsu T, Ohki T, Kishi S, Ogura Y, Takenaka Y, *et al*. Incidence and risk factors of contrast-induced nephropathy after transcatheter arterial chemoembolization in hepatocellular carcinoma. Clin Exp Nephrol 2019;23:1141–1146. doi: 10.1007/s10157-019-01751-4.
31. Nishihara Y, Aishima S, Kuroda Y, Iguchi T, Taguchi K, Asayama Y, *et al*. Biliary phenotype of hepatocellular carcinoma after preoperative transcatheter arterial chemoembolization. J Gastroenterol Hepatol 2008;23:1860–1868. doi: 10.1111/j.1440-1746.2008.05601.x.
32. Hsieh MY, Lin ZY, Chuang WL. Serial serum VEGF-A, angiopoietin-2, and endostatin measurements in cirrhotic patients with hepatocellular carcinoma treated by transcatheter arterial chemoembolization. Kaohsiung J Med Sci 2011;27:314–322. doi: 10.1016/j.kjms.2011.03.008.

33. Sergio A, Cristofori C, Cardin R, Pivetta G, Ragazzi R, Baldan A, *et al*. Transcatheter arterial chemoembolization (TACE) in hepatocellular carcinoma (HCC): the role of angiogenesis and invasiveness. Am J Gastroenterol 2008;103:914–921. doi: 10.1111/j.1572-0241.2007.01712.x.
34. Shim JH, Park J-W, Kim JH, An M, Kong S-Y, Nam B-H, *et al*. Association between increment of serum VEGF level and prognosis after transcatheter arterial chemoembolization in hepatocellular carcinoma patients. Cancer Sci 2008;99:2037–2044. doi: 10.1111/j.1349-7006.2008.00909.x.
35. Xuan Z-D, Zhou L, Wang Y, Zheng X. Prognostic value of the combination of serum levels of vascular endothelial growth factor, C-reactive protein and contrast-enhanced ultrasound in patients with primary liver cancer who underwent transcatheter arterial chemoembolization. Expert Rev Anticancer Ther 2017;17:1169–1178. doi: 10.1080/14737140.2017.1395284.
36. Wang B-M, Li N. Effect of the Wnt/-catenin signaling pathway on apoptosis, migration, and invasion of transplanted hepatocellular carcinoma cells after transcatheter arterial chemoembolization in rats. J Cell Biochem 2018;119:4050–4060. doi: 10.1002/jcb.26576.
37. Zhao ZW, Fan XX, Song JJ, Xu M, Chen MJ, Tu JF, *et al*. ShRNA knock-down of CXCR7 inhibits tumour invasion and metastasis in hepatocellular carcinoma after transcatheter arterial chemoembolization. J Cell Mol Med 2017;21:1989–1999. doi: 10.1111/jcmm.13119.
38. Zhou DY, Qin J, Huang J, Wang F, Xu GP, Lv YT, *et al*. Zoledronic acid inhibits infiltration of tumor-associated macrophages and angiogenesis following transcatheter arterial chemoembolization in rat hepatocellular carcinoma models. Oncol Lett 2017;14:4078–4084. doi: 10.3892/ol.2017.6717.
39. Wu T, Yao Y, Sun R, Wang H, Yin X, Zhang J, *et al*. Arterial infusion of rapamycin in the treatment of rabbit hepatocellular carcinoma to improve the effect of TACE. Open Life Sci 2018;13:299–304. doi: 10.1515/biol-2018-0036.
40. Lin W, Wang H, Zhong M, Yu S, Zhao S, Liang S, *et al*. Effect and molecular mechanisms of Jiedu Recipe on hypoxia-induced angiogenesis after transcatheter arterial chemoembolization in hepatocellular carcinoma. Evid Based Complement Alternat Med 2021;2021:6529376. doi: 10.1155/2021/6529376.
41. Kajihara J, Tomimaru Y, Eguchi H, Yamada D, Wada H, Tomokuni A, *et al*. The clinical impact of transcatheter arterial chemoembolization (TACE)-induced c-Met upregulation on TACE refractoriness in hepatocellular carcinoma. Dig Dis Sci 2016;61:1572–1581. doi: 10.1007/s10620-015-4018-9.
42. Wang H, Rao B, Lou J, Li J, Liu Z, Li A, *et al*. The function of the HGF/c-Met axis in hepatocellular carcinoma. Front Cell Dev Biol 2020;8:55. doi: 10.3389/fcell.2020.00055.
43. Sciarra A, Ronot M, Di Tommaso L, Raschioni C, Castera L, Belghiti J, *et al*. TRIP: a pathological score for transarterial chemoembolization resistance individualized prediction in hepatocellular carcinoma. Liver Int 2015;35:2466–2473. doi: 10.1111/liv.12844.
44. Harada T, Matsuo K, Inoue T, Tamesue S, Inoue T, Nakamura H. Is preoperative hepatic arterial chemoembolization safe and effective for hepatocellular carcinoma? Ann Surg 1996;224:4–9. doi: 10.1097/00000658-199607000-00002.
45. Lu C, Peng S, Jiang X. Effects of preoperative transcatheter hepatic arterial chemoembolization (TAE) on the prognosis of patients with hepatic carcinoma undergoing tumor resection. Zhonghua Wai Ke Za Zhi 1996;34:413–415.
46. Majno PE, Adam R, Bismuth H, Castaing D, Ariche A, Krissat J, *et al*. Influence of preoperative transarterial lipiodol chemoembolization on resection and transplantation for hepatocellular carcinoma in patients with cirrhosis. Ann Surg 1997;226:688–701. doi: 10.1097/00000658-199712000-00006.
47. Lu CD, Peng SY, Jiang XC, Chiba Y, Tanigawa N. Preoperative transcatheter arterial chemoembolization and prognosis of patients with hepatocellular carcinomas: retrospective analysis of 120 cases. World J Surg 1999;23:293–300. doi: 10.1007/pl00013185.
48. Choi GH, Kim DH, Kang CM, Kim KS, Choi JS, Lee WJ, *et al*. Is preoperative transarterial chemoembolization needed for a resectable hepatocellular carcinoma? World J Surg 2007;31:2370–2377. doi: 10.1007/s00268-007-9245-6.
49. Kim IS, Lim YS, Lee HC, Suh DJ, Lee YJ, Lee SG. Pre-operative transarterial chemoembolization for resectable hepatocellular carcinoma adversely affects post-operative patient outcome. Aliment Pharmacol Ther 2008;27:338–345. doi: 10.1111/j.1365-2036.2007.03580.x.
50. Kang JY, Choi MS, Kim SJ, Kil JS, Lee JH, Koh KC, *et al*. Long-term outcome of preoperative transarterial chemoembolization and hepatic resection in patients with hepatocellular carcinoma. Korean J Hepatol 2010;16:383–388. doi: 10.3350/kjhep.2010.16.4.383.
51. Jianyong L, Jinjing Z, Wentao W, Lunan Y, Qiao Z, Bo L, *et al*. Preoperative transcatheter arterial chemoembolization for resectable hepatocellular carcinoma: a single center analysis. Ann Hepatol 2014;13:394–402. doi: 10.1016/S1665-2681(19)30846-4.
52. Yang Y, Lin K, Liu L, Qian Y, Yang Y, Yuan S, *et al*. Impact of preoperative TACE on incidences of microvascular invasion and long-term post-hepatectomy survival in hepatocellular carcinoma patients: a propensity score matching analysis. Cancer Med 2021;10:2100–2111. doi: 10.1002/cam4.3814.
53. Morshid A, Elsayes KM, Khalaf AM, Elmohr MM, Yu J, Kaseb AO, *et al*. A machine learning model to predict hepatocellular carcinoma response to transcatheter arterial chemoembolization. Radiol Artif Intell 2019;1:e180021. doi: 10.1148/ryai.2019180021.
54. Sasaki A, Iwashita Y, Shibata K, Ohta M, Kitano S, Mori M. Preoperative transcatheter arterial chemoembolization reduces long-term survival rate after hepatic resection for resectable hepatocellular carcinoma. Eur J Surg Oncol 2006;32:773–779. doi: 10.1016/j.ejso.2006.04.002.
55. Sugo H, Futagawa S, Beppu T, Fukasawa M, Kojima K. Role of preoperative transcatheter arterial chemoembolization for resectable hepatocellular carcinoma: relation between postoperative course and the pattern of tumor recurrence. World J Surg 2003;27:1295–1299. doi: 10.1007/s00268-003-6817-y.
56. Chen XP, Hu DY, Zhang ZW, Zhang BX, Chen YF, Zhang WG, *et al*. Role of mesohepatectomy with or without transcatheter arterial chemoembolization for large centrally located hepatocellular carcinoma. Dig Surg 2007;24:208–213. doi: 10.1159/000102901.
57. Terasawa M, Allard MA, Golse N, Cunha AS, Cherqui D, Adam R, *et al*. Sequential transcatheter arterial chemoembolization and portal vein embolization versus portal vein embolization alone before major hepatectomy for patients with large hepatocellular carcinoma: an intent-to-treat analysis. Surgery 2020;167:425–431. doi: 10.1016/j.surg.2019.09.023.
58. Yamasaki S, Hasegawa H, Kinoshita H, Furukawa M, Imaoka S, Takasaki K, *et al*. A prospective randomized trial of the preventive effect of pre-operative transcatheter arterial embolization against recurrence of hepatocellular carcinoma. Jpn J Cancer Res 1996;87:206–211. doi: 10.1111/j.1349-7006.1996.tb03160.x.
59. Ren ZG, Lin ZY, Xia JL, Ye SL, Ma ZC, Ye QH, *et al*. Postoperative adjuvant arterial chemoembolization improves survival of hepatocellular carcinoma patients with risk factors for residual tumor: a retrospective control study. World J Gastroenterol 2004;10:2791–2794. doi: 10.3748/wjg.v10.i19.2791.
60. Ha TY, Hwang S, Lee YJ, Kim KH, Ko GY, Gwon DH, *et al*. Absence of benefit of transcatheter arterial chemoembolization (TACE) in patients with resectable solitary hepatocellular carcinoma. World J Surg 2016;40:1200–1210. doi: 10.1007/s00268-015-3373-1.
61. Amisaki M, Honjo S, Morimoto M, Hanaki T, Arai Y, Tokuyasu N, *et al*. The negative effect of preoperative transcatheter arterial chemoembolization on long-term outcomes for resectable hepatocellular carcinoma: a propensity score matching analysis. Yonago Acta Med 2016;59:270–278.
62. Li C, Wang MD, Lu L, Wu H, Yu JJ, Zhang WG, *et al*. Preoperative transcatheter arterial chemoembolization for surgical resection of huge hepatocellular carcinoma (≥10 cm): a multicenter propensity matching analysis. Hepatol Int 2019;13:736–747. doi: 10.1007/s12072-019-09981-0.
63. Ye JZ, Chen JZ, Li ZH, Bai T, Chen J, Zhu SL, *et al*. Efficacy of postoperative adjuvant transcatheter arterial chemoembolization in hepatocellular carcinoma patients with microvascular invasion.

World J Gastroenterol 2017;23:7415–7424. doi: 10.3748/wjg.v23.i41.7415.
64. Wang Z, Ren ZG, Chen Y, Hu J, Yang GH, Yu L, *et al*. Adjuvant transarterial chemoembolization for HBV-related hepatocellular carcinoma after resection: a randomized controlled study. Clin Cancer Res 2018;24:2074–2081. doi: 10.1158/1078-0432.CCR-17-2899.
65. Wang YY, Wang LJ, Xu D, Liu M, Wang HW, Wang K, *et al*. Postoperative adjuvant transcatheter arterial chemoembolization should be considered selectively in patients who have hepatocellular carcinoma with microvascular invasion. HPB (Oxford) 2019;21:425–433. doi: 10.1016/j.hpb.2018.08.001.
66. Wang L, Ke Q, Lin K, Chen J, Wang R, Xiao C, *et al*. Not all hepatocellular carcinoma patients with microvascular invasion after R0 resection could be benefited from prophylactic transarterial chemoembolization: a propensity score matching study. Cancer Manag Res 2020;12:3815–3825. doi: 10.2147/CMAR.S251605.
67. Zhang YF, Guo RP, Zou RH, Shen JX, Wei W, Li SH, *et al*. Efficacy and safety of preoperative chemoembolization for resectable hepatocellular carcinoma with portal vein invasion: a prospective comparative study. Eur Radiol 2016;26:2078–2088. doi: 10.1007/s00330-015-4021-8.
68. Shi HY, Wang SN, Wang SC, Chuang SC, Chen CM, Lee KT. Preoperative transarterial chemoembolization and resection for hepatocellular carcinoma: a nationwide Taiwan database analysis of long-term outcome predictors. J Surg Oncol 2014;109:487–493. doi: 10.1002/jso.23521.
69. Wang L, Yan K, He X, Zhu H, Song J, Chen S, *et al*. LRP1B or TP53 mutations are associated with higher tumor mutational burden and worse survival in hepatocellular carcinoma. J Cancer 2021;12:217–223. doi: 10.7150/jca.48983.
70. Xue M, Wu Y, Fan W, Guo J, Wei J, Wang H, *et al*. Prognostic value of TP53 mutation for transcatheter arterial chemoembolization failure/refractoriness in HBV-related advanced hepatocellular carcinoma. Cancer Res Treat 2020;52:925–937. doi: 10.4143/crt.2019.533.
71. Wang G, Bi C. Correlations of pri-Let-7 gene polymorphisms with the recurrence and metastasis of primary liver cancer after transcatheter arterial chemoembolization. Pathol Res Pract 2018;214:667–672. doi: 10.1016/j.prp.2018.03.022.
72. Hu ZQ, Xin HY, Luo CB, Li J, Zhou ZJ, Zou JX, *et al*. Associations among the mutational landscape, immune microenvironment, and prognosis in Chinese patients with hepatocellular carcinoma. Cancer Immunol Immunother 2021;70:377–389. doi: 10.1007/s00262-020-02685-7.
73. Kim DY, Ryu HJ, Choi JY, Park JY, Lee DY, Kim BK, *et al*. Radiological response predicts survival following transarterial chemoembolisation in patients with unresectable hepatocellular carcinoma. Aliment Pharmacol Ther 2012;35:1343–1350. doi: 10.1111/j.1365-2036.2012.05089.x.
74. Georgiades C, Geschwind JF, Harrison N, Hines-Peralta A, Liapi E, Hong K, *et al*. Lack of response after initial chemoembolization for hepatocellular carcinoma: does it predict failure of subsequent treatment? Radiology 2012;265:115–123. doi: 10.1148/radiol.12112264.
75. Paye F, Jagot P, Vilgrain V, Farges O, Borie D, Belghiti J. Preoperative chemoembolization of hepatocellular carcinoma: a comparative study. Arch Surg 1998;133:767–772. doi: 10.1001/archsurg.133.7.767.
76. Yu YQ, Xu DB, Zhou XD, Lu JZ, Tang ZY, Mack P. Experience with liver resection after hepatic arterial chemoembolization for hepatocellular carcinoma. Cancer 1993;71:62–65. doi: 10.1002/1097-0142(19930101)71:1<62::aid-cncr2820710111>3.0.co;2-8.
77. Kim BK, Kim SU, Kim KA, Chung YE, Kim MJ, Park MS, *et al*. Complete response at first chemoembolization is still the most robust predictor for favorable outcome in hepatocellular carcinoma. J Hepatol 2015;62:1304–1310. doi: 10.1016/j.jhep.2015.01.022.
78. Nagasue N, Galizia G, Kohno H, Chang YC, Hayashi T, Yamanoi A, *et al*. Adverse effects of preoperative hepatic artery chemoembolization for resectable hepatocellular carcinoma: a retrospective comparison of 139 liver resections. Surgery 1989;106:81–86. doi: 10.1002/BJS.1800760836.
79. Wu CC, Ho YZ, Ho WL, Wu TC, Liu TJ, Peng FK. Preoperative transcatheter arterial chemoembolization for resectable large hepatocellular carcinoma: a reappraisal. Br J Surg 1995;82:122–126. doi: 10.1002/bjs.1800820141.
80. Xu W, Kwon JH, Moon YH, Kim YB, Yu YS, Lee N, *et al*. Influence of preoperative transcatheter arterial chemoembolization on gene expression in the HIF-1 alpha pathway in patients with hepatocellular carcinoma. J Cancer Res Clin Oncol 2014;140:1507–1515. doi: 10.1007/s00432-014-1713-4.
81. Si T, Chen Y, Ma D, Gong X, Yang K, Guan R, *et al*. Preoperative transarterial chemoembolization for resectable hepatocellular carcinoma in Asia area: a meta-analysis of random controlled trials. Scand J Gastroenterol 2016;51:1512–1519. doi: 10.1080/00365521.2016.1216588.
82. Kishore SA, Bajwa R, Madoff DC. Embolotherapeutic strategies for hepatocellular carcinoma: 2020 update. Cancers (Basel) 2020;12:791. doi: 10.3390/cancers12040791.
83. Gerunda GE, Neri D, Merenda R, Barbazza F, Zangrandi F, Meduri F, *et al*. Role of transarterial chemoembolization before liver resection for hepatocarcinoma. Liver Transpl 2000;6:619–626. doi: 10.1053/jlts.2000.8312.
84. Sieghart W, Hucke F, Pinter M, Graziadei I, Vogel W, Mueller C, *et al*. The ART of decision making: retreatment with transarterial chemoembolization in patients with hepatocellular carcinoma. Hepatology 2013;57:2261–2273. doi: 10.1002/hep.26256.
85. Zhou Y, Zhang X, Wu L, Ye F, Su X, Shi L, *et al*. Meta-analysis: preoperative transcatheter arterial chemoembolization does not improve prognosis of patients with resectable hepatocellular carcinoma. BMC Gastroenterol 2013;13:51. doi: 10.1186/1471-230X-13-51.
86. Ochiai T, Sonoyama T, Hironaka T, Yamagishi H. Hepatectomy with chemoembolization for treatment of hepatocellular carcinoma. Hepatogastroenterology 2003;50:750–755.
87. Liou TC, Shih SC, Kao CR, Chou SY, Lin SC, Wang HY. Pulmonary metastasis of hepatocellular carcinoma associated with transarterial chemoembolization. J Hepatol 1995;23:563–568. doi: 10.1016/0168-8278(95)80063-8.
88. Ravaioli M, Grazi GL, Ercolani G, Fiorentino M, Cescon M, Golfieri R, *et al*. Partial necrosis on hepatocellular carcinoma nodules facilitates tumor recurrence after liver transplantation. Transplantation 2004;78:1780–1786. doi: 10.1097/01.tp.0000145892.97114.ee.
89. Wu X, Yang C, Yu H, Cao F, Shan Y, Zhao W. The predictive values of serum dickkopf-1 and circulating tumor cells in evaluating the efficacy of transcatheter arterial chemoembolization treatment on hepatocellular carcinoma. Medicine (Baltimore) 2019;98:e16579. doi: 10.1097/MD.0000000000016579.
90. Lee KT, Lu YW, Wang SN, Chen HY, Chuang SC, Chang WT, *et al*. The effect of preoperative transarterial chemoembolization of resectable hepatocellular carcinoma on clinical and economic outcomes. J Surg Oncol 2009;99:343–350. doi: 10.1002/jso.21248.
91. Huang JF, He XS, Lin XJ, Zhang CQ, Li JQ. Effect of preoperative transcatheter arterial chemoembolization on tumor cell activity in hepatocellular carcinoma. Chin Med J (Engl) 2000;113:446–448.
92. An FQ, Matsuda M, Fujii H, Matsumoto Y. Expression of vascular endothelial growth factor in surgical specimens of hepatocellular carcinoma. J Cancer Res Clin Oncol 2000;126:153–160. doi: 10.1007/s004320050025.
93. Li X, Feng GS, Zheng CS, Zhuo CK, Liu X. Expression of plasma vascular endothelial growth factor in patients with hepatocellular carcinoma and effect of transcatheter arterial chemoembolization therapy on plasma vascular endothelial growth factor level. World J Gastroenterol 2004;10:2878–2882. doi: 10.3748/wjg.v10.i19.2878.
94. Mehta N, Fidelman N, Sarkar M, Yao FY. Factors associated with outcomes and response to therapy in patients with infiltrative hepatocellular carcinoma. Clin Gastroenterol Hepatol 2013;11:572–578. doi: 10.1016/j.cgh.2012.12.030.
95. Lei J, Zhong J, Yan L, Zhu J, Wang W, Zeng Y, *et al*. Preoperative adjuvant transarterial chemoembolization cannot improve the long term outcome of radical therapies for hepatocellular carcinoma. Sci Rep 2017;7:41624. doi: 10.1038/srep41624.

96. Xu J, Wang YH, Xia JL, Ge NL, Chen Y, Ye SL. Effect of transcatheter arterial chemoembolization on HBV DNA level in primary liver cancer patients. Ai Zheng 2009;28:520–523.
97. Li X, Zhong X, Chen ZH, Wang TT, Ma XK, Xing YF, *et al*. Efficacy of prophylactic entecavir for hepatitis B virus-related hepatocellular carcinoma receiving transcatheter arterial chemoembolization. Asian Pac J Cancer Prev 2015;16:8665–8670. doi: 10.7314/apjcp.2015.16.18.8665.
98. Peng JW, Lin GN, Xiao JJ, Jiang XM. Hepatitis B virus reactivation in hepatocellular carcinoma patients undergoing transcatheter arterial chemoembolization therapy. Asia Pac J Clin Oncol 2012;8:356–361. doi: 10.1111/j.1743-7563.2012.01534.x.
99. Wang K, Jiang G, Jia Z, Zhu X, Ni C. Effects of transarterial chemoembolization combined with antiviral therapy on HBV reactivation and liver function in HBV-related hepatocellular carcinoma patients with HBV-DNA negative. Medicine (Baltimore) 2018;97:e10940. doi: 10.1097/MD.0000000000010940.
100. Wang X, Yang X, Chen F, Wu S, Song Z, Fei J. Hepatitis B virus reactivation potential risk factors in hepatocellular carcinoma via transcatheter arterial chemoembolization: a retrospective research. Can J Gastroenterol Hepatol 2021;2021:8864655. doi: 10.1155/2021/8864655.
101. Park JW, Park KW, Cho SH, Park HS, Lee WJ, Lee DH, *et al*. Risk of hepatitis B exacerbation is low after transcatheter arterial chemoembolization therapy for patients with HBV-related hepatocellular carcinoma: report of a prospective study. Am J Gastroenterol 2005;100:2194–2200. doi: 10.1111/j.1572-0241.2005.00232.x.
102. Liu DX, Li PP, Guo JP, Li LL, Guo B, Jiao HB, *et al*. Exosomes derived from HBV-associated liver cancer promote chemoresistance by upregulating chaperone-mediated autophagy. Oncol Lett 2019;17:323–331. doi: 10.3892/ol.2018.9584.
103. Gao J, Li XS, Shen W, Wu XC, Feng XX, Ren H. Therapeutic effect and prognosis of interferon therapy after transcatheter arterial chemoembolization in patients with hepatocellular carcinoma associated with hepatitis B virus. Zhonghua Gan Zang Bing Za Zhi 2004;12:460–462.
104. Zeng Y, Mao Y, Shi Z, Zhou Y, Zhang L. Observation of therapeutic effect of I-125 seed implantation combined with chemotherapy and antiviral therapy on HBV-related liver cancer. J BUON 2019;24:1414–1419.
105. Ikeda K, Arase Y, Saitoh S, Kobayashi M, Suzuki Y, Suzuki F, *et al*. Interferon beta prevents recurrence of hepatocellular carcinoma after complete resection or ablation of the primary tumor - A prospective randomized study of hepatitis C virus-related liver cancer. Hepatology 2000;32:228–232. doi: 10.1053/jhep.2000.9409.
106. Kubo S, Nishiguchi S, Hirohashi K, Tanaka H, Shuto T, Yamazaki O, *et al*. Effects of long-term postoperative interferon-alpha therapy on intrahepatic recurrence after resection of hepatitis C virus-related hepatocellular carcinoma - A randomized, controlled trial. Ann Intern Med 2001;134:963–967. doi: 10.7326/0003-4819-134-10-200105150-00010.
107. Zuo CH, Xia M, Liu JS, Qiu XX, Lei X, Xu RC, *et al*. Transcatheter arterial chemoembolization combined with interferon-alpha is safe and effective for patients with hepatocellular carcinoma after curative resection. Asian Pac J Cancer Prev 2015;16:245–251. doi: 10.7314/apjcp.2015.16.1.245.
108. Lin CI, Lin ZY, Hsieh MY, Huang CF, Chen SH, Chuang WL. Potential risk factors for the reactivation of the replication of hepatitis B and C viruses after transcatheter arterial chemoembolization of hepatocellular carcinoma. Kaohsiung J Med Sci 2011;27:554–559. doi: 10.1016/j.kjms.2011.06.029.
109. Wu PZ, Zhou J, Zhang YW. Gelatin sponge microparticles for the treatment of the spontaneous rupture of hepatocellular carcinoma hemorrhage. Exp Ther Med 2016;12:2201–2207. doi: 10.3892/etm.2016.3573.
110. Liu Y, Zhang Y, Bautista D, Tang S, Zhou J, Li C, *et al*. Transarterial p53-gene-embolization with gelatin sponge microparticles for hepatocellular carcinoma with BCLC stage B: single-center experience. Cell Biochem Biophys 2015;71:99–104. doi: 10.1007/s12013-014-0167-2.
111. Jang JH, Lee JW, Hong JT, Jin YJ. Transarterial chemoembolization for hepatocellular carcinoma: an evidence-based review of its place in therapy. J Hepatocell Carcinoma 2015;2:123–129. doi: 10.2147/JHC.S44380.
112. Ao J, Zhang Y, Xu K. Gelatin sponge particle used as an embolic agent in transcatheter arterial chemoembolization treatment for primary hepatocellular carcinoma: its current situation in research. J Interv Radiol 2011;20:1010–1013.
113. Chiang PF, Peng CL, Shih YH, Cho YH, Yu CS, Kuo YM, *et al*. Biodegradable and multifunctional microspheres for treatment of hepatoma through transarterial embolization. ACS Biomater Sci Eng 2018;4:3425–3433. doi: 10.1021/acsbiomaterials.8b00635.
114. Minici R, Ammendola M, Manti F, Siciliano MA, Giglio E, Minici M, *et al*. Safety and efficacy of degradable starch microspheres transcatheter arterial chemoembolization as a bridging therapy in patients with early stage hepatocellular carcinoma and Child-Pugh stage B eligible for liver transplant. Front Pharmacol 2021;12:634084. doi: 10.3389/fphar.2021.634084.
115. Kamran AU, Liu Y, Li FE, Liu S, Wu JL, Zhang YW. Transcatheter arterial chemoembolization with gelatin sponge microparticles treated for BCLC stage B hepatocellular carcinoma: a single center retrospective study. Medicine (Baltimore) 2015;94:e2154. doi: 10.1097/MD.0000000000002154.

How to cite this article: Wei ZQ, Zhang YW. Transcatheter arterial chemoembolization followed by surgical resection for hepatocellular carcinoma: a focus on its controversies and screening of patients most likely to benefit. Chin Med J 2021;134:2275–2286. doi: 10.1097/CM9.0000000000001767