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

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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.

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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. 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.

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

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. 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. Furthermore, TACE has advantages in destroying small tumors and treating satellite nodules; thus, it can help to eliminate micrometastasis lesions that cannot be excised by SR.

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. Lu et al. 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.

Because lipiodol can maintain dense deposition in tumors, some micrometastasis 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. Therefore, TACE helps clinicians to avoid incomplete removal of nodules during SR and thus reduce the risk of early recurrence.

Ren et al. 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 antitumor immune function of patients with HCC.

Detrimental effects of preoperative TACE

Notably, some clinicians indicated that preoperative TACE has detrimental effects. Marukuchi et al. 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. Arslan and Degirmencioglu 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. Nishihara et al. demonstrated that 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. Sergio et al. further found that when TACE is not totally effective, it might induce a significant neoangiogenic reaction and affect patient survival as suggested by an increase in VEGF and basic fibroblast growth factor following treatment. Shim et al. and Xuan et al. 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 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.
invasion and promoting apoptosis of transplanted HCC cells in rats. Furthermore, Zhao et al.\(^\text{[37]}\) 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.\(^\text{[38]}\) 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.\(^\text{[39]}\) 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.\(^\text{[40]}\) 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.\(^\text{[41]}\) 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.\(^\text{[42]}\)

**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.\(^\text{[28]}\) Sciarra et al.\(^\text{[43]}\) 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.\(^\text{[16,44-52]}\) [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.\(^\text{[53]}\)

**Patients with advanced HCC**

Sasaki et al.\(^\text{[54]}\) found that preoperative TACE significantly reduced the 5-year overall survival rate in patients with stage I or II tumors. However, Sugo et al.\(^\text{[55]}\) 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.\(^\text{[53]}\) 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.\(^\text{[56]}\) 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).\(^\text{[32,57]}\) Notably, these studies showing that patients with resectable HCC did not benefit from preoperative TACE were conducted on patients with tumors of <5 cm\(^\text{[3,12,24,45,48,58-62]}\) [Table 2]. In addition, Terasawa et al.\(^\text{[57]}\) 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 >3 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.\(^\text{[53]}\) 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.\(^\text{[63-65]}\) Yang et al.\(^\text{[52]}\) reported that preoperative TACE may achieve a similar effect on patients. Furthermore, Wang et al.\(^\text{[66]}\) 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.\(^\text{[67]}\)

**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
| Reference          | Year | Inclusion period | Country       | Tumor size (cm) | No. of patients | 1/3/5-year DFS (%) | 1/3/5-year OS (%) | p      | p      |
|-------------------|------|------------------|---------------|-----------------|-----------------|---------------------|-------------------|--------|--------|
| No. of patients  | TACE+SR | SR | P | TACE+SR | SR | P | TACE+SR | SR | P |
| Harada et al[44] | 1996 | 1982–1994 | Japan | 98 | 33 | 69.3/77.7/76.0 | 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 | 61.3/81.9/89.2 | 60.8/51.9/36.4 | <0.05 | 88.5/62.9/44.0 | 82.3/53.6/18.6 | <0.05 |
| Matsumoto et al[46] | 1997 | 1988–1995 | France | 49 | 27 | 63.3/63.3 | 63.3/61.1 | NS | NR | NR | NR |
| Lu et al[47]     | 1999 | 1988–1994 | China/Japan | 44 | 76 | 80/30/20 | 80/40/20 | 0.72 | 90/5 S/37 | 90/5 S/37 | 0.75 |
| Chen et al[48]   | 2007 | 1998–2005 | Korea | 117 | 152 | 76.0/57.7/55.1 | 70.9/53.8/48.6 | 0.516 | 75/54/41 | 72/52/39 | 0.516 |
| Kim et al[49]    | 2008 | 1995–2000 | Korea | 97 | 237 | 68/46/46 | 70/49/40 | 0.011 | 75/NR/44 | 89/NR/62 | 0.67 |
| Kang et al[50]   | 2010 | 1997–2007 | Korea | 32 | 64 | 58/36/77 | 77/55/32 | 0.01 | 78/60/26 | 97/83/45 | 0.11 |
| Nishikawa et al[51] | 2013 | 2004–2012 | Japan | 110 | 125 | 73.3/48.9/33.2 | 73.3/29.4/16.3 | 0.062 | 87/46/26,5 | 94.9/79.0/57.8 | 0.647 |
| Lee et al[52]    | 2014 | 2005–2008 | China | 133 | 405 | 76.0/55.7/48.7 | 79.5/61.7/49.6 | 0.205 | 80.9/65.0/54.1 | 83.7/68.9/57.5 | 0.79 |
| Yang et al[53]   | 2021 | 2010–2014 | China | 590 | 1034 | 80.3/55.2/31.9 | 78.2/54.9/37.2 | 0.322 | 93.8/62.8/26.2 | 94.4/68.8/16.6 | 0.27 |

1/2/3-year disease-free survival (%), DFS: disease-free survival; 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 (%) | p      | p      |
|-------------------|------|------------------|---------------|-----------------|-----------------|---------------------|-------------------|--------|--------|
| Reference          | Year | Inclusion period | Country       | Tumor size (cm) | No. of patients | 1/3/5-year DFS (%) | 1/3/5-year OS (%) | p      | p      |
| No. of patients  | TACE+SR | SR | P | TACE+SR | SR | P | TACE+SR | SR | P |
| Yamaseki et al[54] | 1996 | 1987–1989 | Japan | 2–5 | 50 | 47 | 50/33/16.6 | 72.5/54.2 | <0.05 | 85.3/83.5 | 84.8/67.5 | <0.05 |
| Lu et al[55]      | 1996 | 1987–1993 | China | 3–8 | 14 | 33 | 75.0/56.2/36.8 | 78.3/54.2 | <0.05 | 91.4/82.5 | 91.6/83.1 | <0.05 |
| Lu et al[56]      | 1999 | 1986–1994 | China/Japan | >8 | 12 | 18 | 66/54/2 | 78/57/45 | 0.18 | 87/45/5 | 91.6/37 | 0.21 |
| Ren et al[57]     | 2004 | 1995–1998 | China | ≤5 | 77 | 174 | 80/55/32 | 70/52/11 | 0.06 | 93.4/87.5/62.39 | 94.3/79.0/57.8 | 0.395 |
| Chen et al[58]    | 2007 | 1998–2005 | Korea | ≤3 | 108 | 190 | 80/55/5 | 78/55/55 | 0.095 | 89.6/71.8/44.36 | 69.5/49.8/37.40 | 0.0216 |
| Zhou et al[59]    | 2009 | 2001–2003 | China | ≤5 | 30 | 59 | 80/57/44 | 75/55/40 | 0.9 | NR | NR | NR |
| Zhong et al[60]   | 2009 | 2001–2004 | China | ≤5 | 46 | 44 | 80/57/44 | 75/55/40 | 0.9 | NR | NR | NR |
| Yamashita et al[61] | 2012 | 1993–2008 | Japan | ≤5 | 44 | 50 | 80/57/44 | 75/55/40 | 0.9 | NR | NR | NR |
| Hu et al[62]      | 2016 | 2002–2011 | Korea | ≤5 | 105 | 830 | 29.9/17.2/8.9 | 18.3/1.9/1 | 0.003 | 91.3/80.0/46.08 | 94.7/80.9/56.9 | 0.003 |
| Amsa et al[63]    | 2016 | 2004–2012 | Japan | ≤5 | 34 | 87 | 68.7/44.9/44.9 | 90.8/62.6/49.4 | 0.043 | 87.5/62.3/2 | 97.9/93.0/60.5 | 0.043 |
| Li et al[64]      | 2019 | 2004–2014 | China | ≥10 | 88 | 289 | 53.6/32.1/12.6 | 35.7/17.1/7.3 | 0.164 | 78.6/66.4/33.1 | 58.3/34/22.5 | 0.035 |

1/2/3-year disease-free survival (%), 1/3/5/10-year tumor recurrence rate (%), DFS: disease-free survival; OS: not significant; NR: not reported; SR: surgical resection; TACE: transcatheter arterial chemoembolization.
function of some patients with HCC is abnormal. 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. Treatment with branched-chain amino acids to maintain liver function has been shown to optimize clinical outcomes. 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. Thus, severe impairment of liver function is generally considered a contraindication to preoperative TACE. 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. Xue et al. 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. Furthermore, Wang and Bi 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. 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. 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. proposed that the best response could not always be achieved after one session of TACE, especially for large tumors. Georgiades et al. 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. recommended that at least two more TACE sessions should be performed before SR regardless of tumor size. However, Paye et al. suggested that the recurrence rate of HCC also increases with additional TACE sessions. Choi et al. reported that repeated TACE did not increase the incidence of complete tumor necrosis. Furthermore, Yu et al. reported that repeated TACE resulted in tight adhesion of the tumor to the diaphragm and thickening of the hepatoduodenal ligament. Chen et al. 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. 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. 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, Naganas et al. 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. 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. 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. 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.\cite{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.\cite{81} and Kishore et al.\cite{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.\cite{83} Zhang et al.\cite{19} further indicated that tumor necrosis was mainly due to long-term (>20-day) deposition of lipiodol. Sieghart et al.\cite{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.\cite{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.\cite{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 capsule.\cite{85} However, there is increasing evidence that complete tumor necrosis improves the prognosis\cite{46,48,49} (Table 3). In addition, Ochiai et al.\cite{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.\cite{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.\cite{60} The

| Year | Country | Year | Country | Year | Country |
|------|---------|------|---------|------|---------|
| 1997 | France  | 1995-1999 | 1999 | Korea  |
| 1995-2000 | 2000 | 2008 | 2008 | 2008 |

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

- CN: complete tumor necrosis; DFS: disease-free survival; IN: incomplete tumor necrosis; P: P-value for CN vs. IN; OS: overall survival; no-TACE: without TACE.
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\(^{[61]}\) 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-1\(\alpha\), 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 20%, even in highly selected patients.\(^{[48,53]}\) 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.\(^{[17,94,93]}\) 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\(^{[99]}\) reported that TACE might increase the risk of HBV reactivation in HBsAg-negative/anti-Hbc-positive patients diagnosed with unresectable HCC. Wang et al\(^{[100]}\) 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-\(\alpha\) and interferon-\(\beta\) 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-\(\alpha\) 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), 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 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*[116] 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.

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Conflicts of interest
None.

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