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## Review of preoperative transarterial chemoembolization for resectable hepatocellular carcinoma

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published meta-analyses have consistently failed to demonstrate that preoperative TACE improves the prognosis of resectable HCC. We believe that these published articles have several limitations and have our own views about the results of meta-analyses. It is very important that the scientific community shed more light on the pathogenesis of HCC and relate this to choice of therapy. This review mainly concerns our understanding of preoperative TACE for resectable HCC and briefly addresses desirable directions for future studies.

**Key words:** Hepatocellular carcinoma; Surgical resection; Transarterial chemoembolization; Preoperative; Review

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**Core tip:** Hepatocellular carcinoma (HCC) is the sixth most common neoplasm and third most frequent cause of cancer deaths. Resection of HCC offers the only hope for a cure, yet post-resection recurrence is common. The effectiveness of transarterial chemoembolization (TACE) as a neoadjuvant therapy for resectable HCC has not been conclusively demonstrated. All published meta-analyses have consistently failed to demonstrate its effectiveness. We believe these articles have several limitations and TACE is theoretically helpful in multinodular or infiltrative types of HCC.

### Abstract

Hepatocellular carcinoma (HCC) is one of the few cancers whose incidence has been continually increasing over recent years. Resection of HCC offers the only hope for cure. However, recurrences are common in patients who have undergone resection. In our opinion, the effectiveness with which transarterial chemoembolization (TACE) as a neoadjuvant therapy for resectable HCC prevents recurrence and prolongs survival has not been conclusively demonstrated. All

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### INTRODUCTION

Hepatocellular carcinoma (HCC), the commonest

primary liver malignancy, sixth most common neoplasm, and third most frequent cause of cancer deaths, is increasing in incidence and prevalence both nationally and internationally. Potentially curative treatments for HCC include surgical resection, liver transplantation, and local ablative therapy. Among these, hepatectomy is considered the standard treatment for offering a chance of cure to patients with preserved liver function<sup>[1-3]</sup>. However, long-term survival after hepatectomy is unsatisfactory because of the high incidence of tumor recurrence. Even after radical surgery, tumor recurrence occurs in 75%-100% of HCC patients and is their major cause of death. This has led to many efforts to devise effective therapeutic strategies aimed at controlling tumor recurrence and thus prolonging long-term survival after HCC resection<sup>[4]</sup>.

With improvements in interventional radiology, transarterial embolization (TAE) and transarterial chemoembolization (TACE) have been advocated as standard loco-regional palliative treatments for inoperable HCC. Some researchers believe that combining TACE and hepatectomy would improve long-term outcomes. This possibility has generated significant debate and numerous studies of the combination of TACE and curative resection for HCC since it was first described in the early 1990s. Some clinicians have attempted to employ TACE preoperatively as a loco-regional therapy to affect the course of the disease by decreasing tumor size, inducing tumor necrosis and by preventing tumor cell dissemination during surgery. However, others feel that this rationale may not be justified, and if the tumor is already resectable, administering TACE may complicate liver mobilization owing to the perihepatic adhesions that may occur following the TACE procedure<sup>[5-8]</sup>. This review summarizes current published reports linking TACE or TAE with surgical resection of HCC with the aim to suggest generally acceptable guidelines.

## CONTROVERSIAL RESULTS OF PREOPERATIVE TACE

HCC commonly arises in patients with chronic viral or alcoholic liver disease: these patients' livers are likely to harbor multiple and independent clones of premalignant cells and, when these cells are further exposed to carcinogenic insults, unicentric or multicentric carcinogenesis follows. Intrahepatic recurrence can represent either *de novo* tumor formation or intrahepatic metastasis of a clonally identical neoplasm. Early recurrence is primarily attributable to intrahepatic metastases, whereas late recurrence tends to be multicentric in origin. No matter how recurrences occur, it is generally believed that recurrences in the early postoperative period arise not because of inadequate resection of the primary tumor but either because of pre-existing microscopic tumor foci that were not detected by imaging modalities or because of malignant cells that were disseminated during surgical manipulation. Nowadays, the recurrence rate after resection is approximately 50% at 2 years and 75%

at 5 years according to most series<sup>[9]</sup>. If any neoadjuvant therapy reduced the viability of HCC cells and prevented or effectively managed recurrences, the survival after resection of HCC would improve.

HCCs are supplied for the most part by the hepatic artery. Catheter-based techniques take advantage of this unusual architecture to deliver intra-arterial therapy directly to the tumor bed. Thus, TACE induces ischemic necrosis of tumors by arterial injection of chemotherapeutic drugs and embolizing agents. The aims of neoadjuvant therapy are to reduce tumor mass, thus making surgery easier, and destroy microscopic tumor foci and reduce the vascularity of tumors. Preoperative arterial injection of chemotherapeutic drugs and embolizing agents (TACE) reportedly can achieve all of the above-stated aims, as well as reduce the viability of HCC cells<sup>[10-12]</sup>. However, although several studies have demonstrated that preoperative TACE prevents tumor recurrence and prolongs survival in patients with HCC, others have failed to demonstrate these outcomes. Arguments against the use of preoperative TACE include: first, the associated complications, namely, liver function impairment and increased risk of liver failure; second, the associated delay in performing definitive surgery, during which time some resectable tumors become unresectable; third, this form of therapy mainly affects well-differentiated HCC and fails to completely kill poorly differentiated cells, thus the residual HCC cells are more aggressive; and last, incomplete HCC necrosis weakens adhesiveness within the tumor, thus facilitating the release of cancer cells from the primary tumor into the bloodstream. In addition, the effects of preoperative TACE on long-term outcome are controversial: it has not been proven that it prevents tumor recurrence and prolongs survival.

## SYSTEMATIC REVIEW AND META-ANALYSIS

To produce more reliable evidence for clinical decision-making, randomized controlled studies and nonrandomized controlled studies have been subjected to meta-analysis. Several such meta-analyses provide the largest body of information currently available for assessing the role of preoperative TACE in patients with HCC. Their findings are mainly expressed in terms of disease-free and overall survival. To minimize heterogeneity, these studies have utilized strict inclusion criteria. For example, the most recently published meta-analysis, authored by Cheng *et al.*<sup>[13]</sup>, defined cure of HCC strictly as: (1) tumor had been resected; (2) negative surgical margins had been confirmed histologically; (3) no evidence of extrahepatic metastasis; and (4) no residual tumor according to dynamic contrast-enhanced computed tomography or ultrasonography performed 3-5 wk postoperatively. All published meta-analyses have failed to show that preoperative TACE improves the prognosis<sup>[14-19]</sup>. Although the cited meta-analyses are well designed and conducted, and, more importantly, have reported consistent findings, we

believe it is prudent to recommend TACE as a routine preoperative procedure for resectable HCC for the reasons explained below.

## NEW QUESTIONS AND IDEAS

Although the mechanisms of recurrence after surgical resection of HCC remain controversial, it is noteworthy that early recurrence mainly takes the form of intrahepatic recurrence, which correlates strongly with tumor-related variables, whereas late recurrence mainly takes the form of multicentric foci, this correlating strongly with the condition of the remnant liver. Relevant tumor-related variables include vascular infiltration, tumor size, tumor capsule, and satellite nodules or dissemination of tumor cells during hepatectomy. Thus, both main tumor and the surrounding tissue may contain detectable or undetectable satellite nodules and the main route of early post-resection intrahepatic recurrence is spread *via* the portal vein. Clearly, hepatectomy cannot address all of these possibilities. In theory, TACE could; however, published meta-analyses studies do not support this contention<sup>[20-23]</sup>.

However, the available studies have several limitations. We have found that the various meta-analyses use very heterogeneous definitions of resectable HCC. They also use different definitions of cure of HCC and different inclusion criteria. Thus, their findings indicate only that preoperative TACE does not improve the prognosis of resectable HCC as defined in that particular study.

Morphologic types of HCC include focal/nodular, massive, and diffuse/infiltrative. The infiltrative type accounts for 7%-15% of HCC cases. Although infiltrative HCC is not uncommon, especially in regions where hepatitis B virus is predominant, there are few published data concerning treatment of patients with this variant because infiltrative HCC almost always presents as an advanced diffuse tumor and surgery is therefore rarely indicated. The cumulative survival rates of patients with infiltrative HCC are reportedly 33.3% at 1 year and 13.6% at 3 years, independent of the treatment received<sup>[24-27]</sup>. About 15.9 % of reported patients with infiltrative HCC have undergone TACE repeatedly, with curative intent, and have survived more than 2 years. These long-term survivors are over 60 years old, have preserved hepatic function at the time of initial diagnosis, and have a major portal vein thrombosis without parasitic supply. In addition, published studies have also ignored the multinodular type of HCC<sup>[28-31]</sup>. Taking these observations into consideration allows the following improved understanding of the findings of published meta-analyses. First, TACE would indeed be helpful for treating small satellite nodules and destroying microscopic tumor foci, thus facilitating achievement of adequate resection, which would prolong the duration of survival. However, these considerations apply only in certain types of HCC, namely, to the best of our knowledge, multinodular and infiltrative types. Second, these are not the main types and have often been excluded from published meta-

analyses. In conclusion, we still provocatively recommend preoperative TACE for resectable HCC, especially for multinodular and infiltrative types, to reduce recurrence rates. We also believe it is prudent to recommend TACE for patients with definite single nodular or massive HCC. We also recommend assessing the effects of preoperative TACE according to the various morphologic types.

## CONCLUSION

We still cannot be certain whether preoperative TACE for resectable HCC is beneficial. Although we believe it is helpful in multinodular or infiltrative types of HCC, there is limited evidence for this. We believe it makes sense to assess the effects of preoperative TACE according to the various morphologic types. Thus, larger, well designed, randomized clinical trials are needed to detect realistically achievable treatment benefits.

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