CURRENT STATUS OF TRANSCATHETER ARTERIAL CHEMOEMBOLIZATION FOR HEPATOCELLULAR CARCINOMA

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ABSTRACT

Hepatocellular carcinoma (HCC) is a lethal disease that kills hundreds of thousands of people each year worldwide. Transcatheter arterial chemoembolization (TACE) is a widely used approach in clinical practice to treat HCC. Many patients with unresectable HCC benefited from this technique. Now, TACE has evolved into the first choice among non-surgical HCC’s for its minimally invasive nature and definite therapeutic effects. However, this technique was beset with relative high incidence of complications plus low cure rate. For optimal TACE’s antitumor effect, many efforts have been made in varies aspects of TACE procedure including alterative contrast agent, combination therapies, newly developed embolizing agents and evaluation techniques et al. Therefore, this paper reviews recent advances in TACE for HCC, highlighting newly developed embolization agents and TACE-based integrated therapies in an attempts to improve local curability which may help to get closer to ultimate success of HCC treatment.

Keywords: Transcatheter arterial chemoembolization, Embolization agents, Hepatocellular carcinoma, Combination therapy, Treatment outcome.

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Introduction

Surgical resection used to be the main method to treat hepatocellular carcinoma (HCC). However, since transarterial chemoembolization (TACE) was first reported by Goldstein in 1976, it has been adopted worldwide to prolong the survival of HCC patients, and more patients with unresectable HCC have benefited from this technique. Now, TACE has evolved into the first choice among non-surgical treatments of HCC because of its minimally invasive nature and definite therapeutic effects¹⁻³. Usually, practitioners manipulate to deploy a delivery system (catheter) into the target arterial (blood supply of the liver tumor) with the aid of digital subtraction angiography (DSA), thereafter, introducing embolizing materials (plus drugs on most occasions) through the catheter to eliminate the tumor by occluding its arterial supply. Samples obtained from the occluded region identify necrosis of tumor tissue⁴. Theoretically, arterial administration of anticancer drugs is more effective than systemic administration because drug concentration is higher in the local region while systemic concentration is low⁵.

Although, it’s controversial that whether the transarterial embolization (TAE) is as effective as TACE, most practitioners prefer TACE for theoretically stronger tumor control both in liver and possible metastasis elsewhere. Researchers have compared several anticancer drugs(doxorubincin, cisplatin, epirubicin and mitomycin et al.) often used in TACE and the result was no chemotherapeutic agent was better than any other.
Unfortunately, there was no significant progress in this field recently\(^9\).

Nowadays, TACE is the first choice for patients with compensated liver function and large multifocal lesions without evidence of vascular invasion or extra-hepatic spread\(^4\). Despite the high incidence of local tumor recurrence (compared to surgical resection or radiofrequency ablation (RFA)), TACE does improve survival times (compared to supportive care or sub-optimal therapies), observed as an increase in the 3-year survival rate to 26-73%\(^3,6,7\).

**Role of TACE in treatment of HCC**

Defined as a palliative method for the treatment of HCC, TACE was previously the second choice when liver resection, RFA and liver transplantation were all impossible. However, Kim et al\(^8\) found that there was no significant difference in OS between the effectiveness of TACE and RFA for stage 0 HCC, although RFA showed a better tumor response and longer time to progression (TTP). TACE may be considered a viable alternative to RFA for treating single HCCs that are \(\leq 2\) cm when RFA is not feasible.

Complete response after a single session of conventional TACE is rare. For consistent control, additional TACE is suggested to pre-schedule depending on each previous response\(^9\). Considering recurrent tumors are mostly supplied by feeders from the adjacent segmental arteries and arterial recanalization\(^10\), it is usually recommended that patients are evaluated every 3-12 wk, and additional TACE sessions are planned if enhanced imaging reveals tumor activity in follow-up. For optimal results, usually two to four procedures are performed. Thereafter, repeated tumor biomarkers (\(\alpha\)-fetoprotein; abnormal prothrombin et al.) and imaging studies are used to monitor tumor progression.

The role of TACE for patients at different stages of HCC is quite different. According to the Barcelona-Clinic Liver Cancer (BCLC) classification, only intermediate-stage HCC were suggested to TACE for longer survival time and better quality of life. However, since it has been clinically proven that the TACE can safely lead to not only reduction in tumor size but also good relief of cancerous pain. Interventional radiologists occasionally use TACE on patients with HCC at advanced or terminal stage to lessen their pain for better life quality when symptomatic treatment doesn’t work well while the survival time of those patients usually can’t be prolonged. As to patients of early stage HCC, TACE has proved to be not inferior to those traditional curative methods as RFA and liver surgery\(^9,11\). So, TACE can also achieve excellent results in treatment of selected HCC patients at early stage. However, when TACE is initially performed to these patients, special care should be taken to surveillance for tumor recurrence to make sure complete response. In addition, TACE can be also used to downstage HCC to meet Milan criteria in selected patients and bridging tool before liver transplantation.

Complications are not rare after TACE. Elevated alanine aminotransferase is the most common, with a rate of ~85%. The second most common is post-embolization syndrome that consists of transient abdominal pain and fever (60-80%) and usually self-limiting within 3-4 d\(^12\). Acute liver decompensation (jaundice, encephalopathy or ascites) is reported in only 0.1-3% of procedures. Biliary (subcapsular biloma, focal strictures of the common hepatic or bile duct, and diffuse dilatation of the intrahepatic ducts) and gastrointestinal (gastritis, ulceration and bleeding.) complications have been reported in 0.5-2% and 0-22% (median 3%) of patients, respectively. Irreversible hepatic decompensation, defined as deterioration of liver function, that does not recover to the pretreatment level is found in 3% of patients. Acute renal failure has been reported at 8.6% and 1.8% (range 0-13%) is irreversible that is frequently associated with diabetes\(^12\).

Other complications including liver abscesses in patients with an incompetent ampulla of Vater, vascular injury from repeated intra-arterial chemotherapy, and tumor rupture are rare. The most fatal complication is tumor rupture, which is responsible for almost all the sudden death after TACE. Furthermore, compromised liver function, tumor thrombi in the main portal vein, biliary tract obstruction, history of bile duct surgery, overdose of embolic agents, hepatic artery occlusion due to repeated TACE, and nonselective TACE will lead to increased complication rates\(^11,13\). The benefits of TACE should be better balanced with these risk factors before the procedure. So, the prognosis of HCC at an early stage is better after TACE.

The selection of TACE candidates is mainly based on liver functional reserve. Some experts have recommended a series of absolute and relative contraindications for TACE, including large tumors,
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reduced or absent portal vein flow, biliary obstruction and hepatic encephalopathy\(^{(9)}\), because under these conditions, occlusion of tumor arterial supply may induce liver failure. In contrast, there were uncontrolled trials and cohort studies that suggested the benefit of TACE in selected patients with the above conditions\(^{(18-22)}\). A meta-analysis including eight studies with 1601 patients even concluded that TACE could improve the 6-mo and 1-year survival of patients with portal vein thrombosis compared with conservative treatment\(^{(15)}\). In Japan, TACE is recommended for those patients with portal invasion if only it is below the second portal branch\(^{(2)}\). So, with improved techniques and advanced equipment, more absolute contraindications for TACE will become relative ones in the future which should explain in some degrees why there are differences in indications of TACE among countries.

**Recent progresses in research of TACE techniques**

Conventional iodinated contrast DSA (C-DSA) is potentially nephrotoxic and allergenic, however, carbon dioxide DSA (CO2-DSA) is non-nephrotoxic and non-allergenic. Because of the adverse effect of vapor lock and low-quality vascular images, CO2-DSA is usually used in the liver, peripheral arteries and abdominal aorta, but not in cerebral angiography\(^{(16)}\).

Minami et al investigated if balloon-occluded TACE (b-TACE) produced a better iodized oil accumulation than conventional TACE in various stages of HCC, but there was no significant difference\(^{(17)}\).

Because traditional radiotherapy may lead to external beam over-exposure of the liver and eventually a clinicopathological syndrome, minimally invasive transarterial radioembolization (TARE) has emerged. Unlike TACE, the embolic particles used in TARE are loaded with a radioisotope. The most commonly used radioisotope is yttrium-90. Radioembolization has limited tissue penetration, which allows for high local dose of radiation within the tumor, but less risk of radiation-induced injury in liver tissues nearby. Different from the particles (> 100 µm) used in TACE, smaller particles (25–35 µm) are used in TARE to reach the tumor microvasculature\(^{(18-22)}\).

A study comparing TACE and TARE reported that TACE had a higher rate of abdominal pain, diarrhea and elevation of aminotransferases, while fatigue and fever were more frequent after TARE\(^{(22)}\).

Overall, compared to TACE, TARE had higher response rate (49% vs. 36%, \(P = 0.052\)) and longer TTP (13.3 vs. 8.4 mo, \(P = 0.046\)), but not longer median survival time (20.5 vs. 17.4 mo, respectively, \(P = 0.232\)) and OS (18-20). So, the lack of survival improvement plus the cost associated with radioembolization restrict the application of this technique.

To minimize the harm caused by the guiding X rays during TACE procedure, robot-assisted catheter inserting or an alternative monitoring system that does less or no harm are expected in the future.

The core technique of TACE is still and will always be super-selection. Early in 1993, Matsui et al proved that sub-segmental TACE was superior to TACE\(^{(23)}\). The improvements in TACE techniques are listed in Table 1.

Usually, transcatheter vascular occlusion is achieved by using embolization agents such as lipiodol, gelatin sponge, starch microspheres, polyvinyl alcohol (PVA) beads, or collagen particles. Some embolization agents such as PVA polymer are not biodegradable. To allow repeated transcatheter therapy, biodegradable agents, such as gelatin sponge and starch microspheres are preferred. Small embolization agents (<100 µm) that have the ability to embolize end-branches of the hepatic artery and prevent development of collateral arterial flow are favored. An early study revealed that particle size > 40 µm diameter is because smaller particles might the penetrate liver capillary system and lead to non-target embolization, such as lung and spleen\(^{(24)}\).

However, when particle size is > 1000 µm, they are more likely to cause catheter clogging. Usually, slower infusion of more diluted suspension means more-distal arterial occlusion\(^{(25)}\). The elasticity and shape of the particles also play a role; embolization particles with irregular surfaces tend to lodge in larger diameter vessels compared with regularly surfaced particles, and particles with a high degree of elasticity are more likely to reach deeper in vessels\(^{(30)}\).

Reflux is one of the complications that manipulators want to avoid most during intra-arterial embolization, because it can lead to unwanted embolization of areas nearby or even other non-target vital organs. Generally, large particles with rapid injection and overloading increase the risk of reflux and non-target embolization\(^{(25)}\). Reducing injection rate decreases the risk of reflux and non-
target embolization. To minimize adverse effects of TACE, the use of calibrated particles (PVA or spherical embolic agents) is increasing worldwide because they can be chosen by size and amount according to the target vessels\(^{(20)}\).

Lipiodol (Lipiodol Ultra Fluid, Guerbet, Roissy, France), also known as ethiodized oil, is an oily contrast medium with an iodine content of 38% by weight. Nowadays, it is the most frequently used embolization agent in TACE procedures because of the following characteristics.

First, it is opaque to X-rays, so, we can track and map the agent that can be delivered during injection. In this way, we can assess the degree of occlusion of target arteries and stop unwanted embolization.

Second, Lipiodol has tumor-seeking properties. When injected into the hepatic artery, most Lipiodol selectively accumulates in tumor nodules. Patients with heterogeneous Lipiodol uptake on computed tomography (CT) scan can have a greater tendency to recurrence during follow-up than those with homogeneous uptake, and the degree of Lipiodol deposition is an independent prognostic factor\(^{(29,30)}\).

Third, embolization of Lipiodol is transient and plastic. It is eventually washed out from the target region within several weeks to over a year due to a siphoning effect from hypervascularization of the tumor vessels and the absence of Kupffer cells inside the tumor, which is thought to facilitate repeated intra-arterial treatment. Last, Lipiodol is cheap compared to other embolic agents. Lipiodol masks assessment of residual vascularity on CT imaging, so routine follow-up for possible remnant tumor with contrast-enhanced magnetic resonance imaging (MRI) has been suggested instead of CT for those TACE protocols involved with Lipiodol.

In addition, because of the oily nature of Lipiodol, it distributes in both the tumor artery branches and the peritumor portal venules, which makes transient dual embolization of the tumor possible\(^{(31)}\). Theoretically, this dual embolization means dual tumor blood supply occlusion and results in better tumor control.

As Lipiodol is opaque to X-rays, it can also be used as a vehicle to carry and mark anti-cancer drugs inside the tumor. To improve both the concentration and working times of cytotoxic drugs within the tumor, the so-called “lipiodolization” technique is used. Currently, a broad spectrum of anti-cancer drugs is used to mix with Lipiodol.

It is suggested that the mixture is prepared at the time of use and used promptly after preparation. When the mixture of Lipiodol and the drug is injected into the arteries supplying a tumor, the

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Table 1: Advances in TACE techniques.

NR= not reported

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anti-cancer drug is slowly released from the Lipiodol and remains at a high concentration within the tumor for a prolonged period. Studies have shown that Gelfoam embolization can facilitate the slow release of doxorubicin from Lipiodol, hence further increasing the drug concentration inside the tumor by preventing washout of the mixture\(^{(32)}\). Usually, Gelfoam is applied immediately after injection of the Lipiodol formulation into the hepatic artery.

To meet various clinical demands, practitioners have tried to develop new formulations in vitro, the Lipiodol-pirarubicin mixture proved to be more effective and more stable than classical doxorubicin-Lipiodol mixture\(^{(33)}\). SM-11355 is another novel lipophilic platinum complex, which is a derivative of cisplatin developed for preparation of Lipiodol suspension. The sustained release properties of this formulation mean that TACE can obtain a lower plasma platinum concentration plus a prolonged half-life\(^{(34)}\). However, not all chemical drugs can be used to make this formulation. Hydroxycamptothecine, for instance, cannot make this drug-Lipiodol mixture. This might correlate with the interaction between the drug and lipiodol.

Gelatin sponge is another commonly used embolization agents. Particle sizes are typically in the range of 0.5-2 mm or bigger, depending on the target arteries. The vessel occlusion by gelatin sponge is temporary, and recanalization occurs within a few days to weeks. As Gelfoam particle size tends to be of millimeters, the particles clump in the larger arteries and not the small tumor supply vessels. Powder of gelatin sponge is produced to reach smaller vessels to achieve more distal and lethal embolization. However, as gelatin powder can go much deeper into tissues, adverse effects of non-targeted embolization are more likely to occur. For this reason, it was removed from the US market in 2000\(^{(24)}\).

Different from gelatin and lipiodol, PVA particles were designed to cause permanent or semi-permanent vessel occlusion. PVA particles are varied in size and shape and tend to clump occasionally, which might cause catheter clogging. To fit various sizes of arteries, the size range of PVA is 100-1200 µm\(^{(35)}\). However, no evidence proves that PVA-TACE is superior to lipiodol-TACE or gelatin-TACE for OS\(^{(36)}\).

To overcome the weak point generated with irregular particle size and shape, researchers have developed spherical particles. Embosphere is such an embolic agent marketed by Merit Medical (Rockland, MA, USA). It is a permanent agent with calibrated size ranges. Compared to PVA, Embosphere has a smooth hydrophilic surface, deformability and lack of aggregation, therefore, Embosphere can embolize deeper and smaller vessels\(^{(37)}\). However, its mechanical profile still does not lead to better clinical results.

Embozene (CelNovo BioSciences Inc., Atlanta, GA, USA) is another long-acting embolizing agent that was designed to be anti-inflammatory and resistant to bacteria\(^{(38)}\). Embozene has the most tightly calibrated sizes, namely 100, 250, 400, 500, 700, and 900 µm. Each size has 95% of the particles within 50 µm of the nominal size. However, whether tightly controlled particle size brings additional clinical benefits for embolization is still controversial.

Some studies have suggested that temporary embolizing agents can cause fewer post-embolization syndromes\(^{(39)}\). So it comes the shorter-duration, degradable starch microspheres (Spherex, Magle Life Science, Sweden; EmboCept, Pharmaceut, Germany). Spherex consists of sterilized starch microspheres suspended in saline solution and provides transient occlusion of small vessels.

Lipophilic cytotoxic drug complexes are unstable and have to be prepared just before injection, therefore, more convenient, non-resorbable microspheres loaded with cytotoxic drugs have been developed. These particles are termed drug-eluting beads (DEBs) and were designed to sequester doxorubicin from solution and release it in a sustained manner. In this way, the systemic dose of chemotherapeutic agents can be substantially reduced while sharply increasing local drug concentration\(^{(40)}\).

DEB is a novel drug delivery system for embolization, comprising biocompatible, non-resorbable PVA microspheres doped with sulfonyl groups, resulting in a static charge leading to reversible ionic binding with polar molecules such as doxorubicin. It is the structure that allows the DEBs to release the cytotoxic drugs in a sustained manner, which subsequently increases the local concentration of the drug with lower systemic toxicity. A subsequent study revealed a dose-response relationship between the loading and releasing of doxorubicin. When the 500-700-µm beads were used, it was found that the half-life increased from 381 to 3658 h as the concentration of doxorubicin load increased from 6.25 to 37.5 mg/mL\(^{(41)}\).
A rabbit liver VX-2 tumor model confirmed that a high level of doxorubicin in the tumor was achieved over the entire 14-d study period and the high level was associated with widespread necrosis of the tumor tissue\(^{(42)}\). The size of the DEBs was selected based on the anatomy of the feeding vessels as usual. It is recommended to choose smaller (100-300 or 300-500 µm) particles first, followed by larger (500-700 µm) particles until stasis in the target vessel is achieved. In the case of diffuse tumors, lobar or segmental embolization is suggested. When it comes to hepatic vein shunting, larger particles or steel coils are used to avoid the risk of non-targeted pulmonary embolization. While the drug diffusion of DEBs relies on passive release from the carrier, a delivery system that can actively release the drug payload (e.g., via heat/magnetic triggered release) might enhance the flexibility of the dosing regimen and potentially improve the efficacy of the treatment. A meta-analysis compared TACE using doxorubicin-loaded DEBs with conventional TACE and demonstrated a significant reduction in liver toxicity and drug-related adverse events. However, there was still no significant difference in clinical efficacy between DEB TACE and conventional lipiodol-based TACE\(^{(43)}\).

Other DEBs, dry HepaSphere (BioSphere Medical, Roissy en France, France) are supplied in several sizes, namely, 50-100, 100-150 and 150-200 µm. The size varies under different conditions: ~2 and ~3.5 times the original diameter in ionic contrast media and ~4 times in human serum\(^{(44)}\).

Based on the interest in DEBs, the vendor (BTG, Surrey, UK) has developed irinotecan-eluting beads for the treatment of liver metastases from colorectal cancer\(^{(45)}\). However, a randomized controlled trial (RCT) and clinical investigation of irinotecan-eluting beads did not find significant improvement of clinical outcomes\(^{(46,47)}\). A similar product in China is named CalliSphere (Suzhou Callisyn BioMedical Incorporation). It is colored blue and has a similar mechanical profile and clinical result as above.

Compared to conventional TACE, DEB-TACE is generally well tolerated and has minor adverse events. It has a better pharmacokinetic profile that results in fewer drug-related systemic adverse events\(^{(48)}\). For optimal DEB effects in TACE, physicians have tried to standardize the procedure to make the use of DEBs more appropriate and consistent\(^{(49)}\). These general guidelines include pretreatment imaging, peri-procedural medication, choice of bead size, planned dose of doxorubicin, loading dose of doxorubicin, bead dilution, catheter positioning, injection rate, and embolization end-point. However, the decision-making process includes so many tumor- and patient-related factors plus the complexity of HCC; therefore, it may be more applicable to follow a customized/non-standardized approach.

**TACE-based integrated therapies**

O’Suilleabhain et al\(^{(50)}\) evaluated the long-term survival of TACE in patients with unresectable HCC and concluded that a cure for unresectable HCC is possible but rare with TACE (2%). However, TACE after radical excision of HCC can definitely destroy remnant cancer cells, decrease recurrence rate and increase survival rate. TACE before resection of HCC can also obtain a survival advantage when compared with resection alone\(^{(51)}\). In addition, being the most accurate method for detection of liver tumors, preoperative TACE is helpful for detection of multiplicity that was crucial for treatment protocol decision. Therefore, it’s seemed that preoperative TACE should be suggested to all HCC who are scheduled liver surgery.

It is now widely accepted that RFA is equally safe and effective for liver resection for a single HCC up to 5 cm in diameter and has been listed as a first-line treatment in such a condition\(^{(52)}\). However, the local tumor progression rate, an important prognostic factor for RFA-treated HCC, sharply increases when tumors exceed 3 cm in size\(^{(53,54)}\). Notably, it is almost impossible to achieve complete ablation in tumors > 5 cm because the ablation zone is limited\(^{(55,56)}\). Kim et al\(^{(57)}\) compared the safety and effectiveness of combined RFA and TACE with RFA alone in the treatment of mid-sized HCC (3-5 cm). In the combined therapy group, the long-term local tumor progression rates were significantly lower than that of RFA alone (1-, 3-, 5- and 7-year local tumor progression rate: 9, 40, 55 and 66% vs. 45, 76, 86 and 89%, respectively; all P < 0.001).

The observed advantages appear to be attributed to the reduced heat-sink effects by significantly decreasing the tumor arterial flow and enhancing the ablation effect within the ablation zone. This enhancement eventually leads to more microscopic satellite tumor control\(^{(58-64)}\). A similarly conclusion was reached in another RCT that combined RFA with TACE and RFA: the local tumor progression rate was 6% versus 39% at the end of 3 years\(^{(65)}\).
Minimally invasive thermal ablation techniques (RFA, cryoablation or hyperthermic ablation) are associated with the local release of tumor antigens that may enhance host immunity and theoretically eliminate more remnant tumor cells (64). This immunological enhancement makes combination therapy with TACE and minimally invasive thermal ablation more effective.

Combination of TACE with percutaneous ethanol injection (PEI) has been shown to be more effective than TACE alone for unresectable HCC. The 3-year survival rate was longer in patients treated with a combination of TACE and PEI than with TACE alone (22% vs. 4%, respectively) (65).

Combination of TACE with 131I-metuximab (Licartin; Chengdu Hoist Hitech Co. Ltd., Chengdu, China) can prolong the survival time even in patients with advanced HCC compared with TACE alone (12-mo survival rate 60.49 vs. 34.44%) (66).

Combination of TACE with radiotherapy was proved to have better 1-year survival and complete response (odds ratio 1.36 and 2.73). However, the patients had an increased incidence of gastroduodenal ulcers and elevated levels of total bilirubin and alanine transaminase (67).

Combination of gene or para-toluensulfonamide (PTS, a unique anti-tumor agent in liquid forms) with TACE has also been reported to be effective for unresectable HCC. We managed to treat unresectable HCCs with TACE combined with H101 (a recombinant human type 5 adenovirus) and PTS after TACE failure to control them alone. We conclude that combination therapies might still be safe and effective in these patients. Two cases reported were both cured by combination treatment (67,68). Further study with more cases might facilitate the introduction of these two anti-cancer agents as a novel modality for the treatment of HCC with TACE.

Local administration of dendritic cells during TACE in HCC patients has been found to be safe and to prolong recurrence-free survival compared with TACE alone (64). Currently, combination of TACE with other immunotherapies, such as anti-programmed death (PD)-1 or chimeric antigen receptor T cell therapy, for treatment of HCC is making progress. Other researchers have observed that aspirin prolonged OS (median 32.5 vs 20.3 mo) in patients who underwent TACE. However, the mechanism is still unclear. It is thought that the anti-tumor effect of aspirin may be correlated to inhibition of cyclo-oxygenase-2 activity and enhancement of the sensitivity of cancer cells to anticancer drugs (69).

Not all results are positive, and Lei Liu et al showed that combination of TACE and sorafenib only prolonged TTP and not OS (8).

**Techniques for evaluation of TACE treatment outcome**

Early assessment of TACE effectiveness and monitoring of tumor response are critical for identifying failed procedures, guiding therapy, and determining the optimal interval for repeat treatments. Some authors point out that Response Evaluation Criteria in Solid Tumors (RECIST) cannot fulfill the demands of assessment of TACE effectiveness because they only rely on tumor size as the measure of tumor response, which does not consider the tumor necrosis level (70). The anti-cancer activity of TACE eventually leads to tumor size reduction and tumor necrosis, which can be revealed by contrast-enhanced imaging. Thus, RECIST have been modified, based on the diameter of the target lesions and viable tumor. So, mRECIST should better evaluate patients who undergo TACE or TARE.

AFP is a widely used prognostic biomarker to evaluate clinical response of HCC to TACE. It is only valuable in predicting response of patients with a high level of serum AFP. AFP in those patients decreases after TACE, indicating a positive response. Otherwise, its predictive efficacy is poor. However, this is not reliable because ~30% of HCC patients have no elevated AFP, and monitoring of AFP cannot substitute for dynamic imaging studies of the lesion. Cellular lysis may induce immediate elevation of AFP after TACE, which is not reflective of disease progression. So, it should not be used to assess response in the acute setting.

Wang et al (71) found intra-procedural tumor perfusion reduction during chemoembolization associated with transplant-free survival of HCC patients, and suggested that transcatheter intra-arterial perfusion MRI can be used as an intra-procedural imaging biomarker to assess tumor perfusion reduction.

Similarly, researchers (72,73) used the intra-procedural C-arm dual phase cone-beam computed tomography (DP-CBCT) immediately after TACE with DEBs to predict HCC tumor response 1 mo later. They found that it was superior to DSA in detecting tumor nodules plus feeding arteries and there was a significant relationship between tumor
enhancement seen at DP-CBCT after TACE and follow-up MRI response 1 mo later. So, they suggested DP-CBCT to predict tumor response after TACE.

In Sahani’s opinion, perfusion MRI is superior to mRECIST and RECIST in predicting early tumor response to TACE. Other functional imaging methods, such as 18-F-fluorodeoxyglucose positron emission tomography (PET)/CT and contrast-enhanced ultrasound have been used to assess post-treatment efficacy. However, researchers found that contrast-enhanced ultrasound may occasionally miss small residual tumor nodules and only intermediate-stage HCC is eligible for PET/CT.

Patients who show no tumor response shortly after TACE usually have a worse prognosis. If satisfactory tumor necrosis is not achieved after the first session of TACE, a second attempt is suggested because feeding arteries may have been missed. However, patients that do not respond to consecutive session of TACE twice should be considered for alternative therapies.

**Failure of TACE**

There is no consensus for TACE refractoriness, nor when to consider TACE failure and suggest alternative therapy. However, when patients show poor tolerance or adverse reaction after the first or second session of TACE, alternative therapies such as sorafenib or immunotherapy (anti-PD1 or PD-ligand 1 et al.) may be helpful. Repeated TACE should be considered based on the mRECIST result of the last TACE session and the risk of adverse events. The response to the first TACE session and its effect on the underlying liver disease help to identify whether and in how much degree patients are at risk of adverse outcome with repeated TACE. A so-called ART score (assessment for retreatment with TACE) is used to evaluate the safety plus necessity of repeated TACE. Sieghart et al conducted a multivariate analysis to investigate whether patients can benefit from the second or third session of TACE by incorporating three prognostic factors: 4 points for an aspartate aminotransferase increase by 25%; 1.5 or 3 points for a Child-Pugh class increase of 1 or at least 2 points, respectively; and 1 point for the absence of radiological tumor response. Patients with an ART score of 0–1.5 points would have more chance to benefit from a second TACE session, whereas those with a score ≥ 2.5 would not. However, some well-known homogeneous characteristics (such as time assessment of the lab, tumor burden et al.) were not enrolled in this score system. So, ART has not been wildly accepted in clinical since we have already over 10 criteria, including Child-Pugh, BCLC et al. which were not inferior to it.

**Conclusion**

We are now facing many challenges in the field of improving the survival outcomes of TACE in the treatment of HCC. The most difficult challenges are how to detect HCC at an early stage and timely eliminate the remnant tumor cells as much as possible, and prevent recurrence of HCC after TACE. The remnant tumor tissue and recurrence of HCC after TACE are the two main factors that lead to a poor therapeutic effect. The two factors are also the main causes of tumor-related deaths in patients with HCC. A high potential of invasion and metastasis often exists in spite of the tumor being small and at an early stage. The high incidence of HCC recurrence is closely associated with both the characteristics of the tumor and the effect of TACE.

Recently, much attention has been paid to research of biological properties of HCC, including common material and structure basis, proliferation, stress response, growth, development, metabolism, genetics and variation, and the adaptation to and impact on the tumor microenvironment. We are looking forward to seeing more breakthroughs applied in TACE in the future.

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