

A review of applying transarterial chemoembolization (TACE) method for management of hepatocellular carcinoma

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ABSTRACT

Liver cancer is one of the most ordinary reasons for death among cancers. Hepatocellular carcinoma (HCC) is the most common type of liver cancer. In spite of the fact that various remedial methods have been approved particularly the survival effects of the transcatheter arterial chemoembolization (TACE) method have been accomplished widely in the HCC treatment. By applying the TACE method correctly, good survival outcomes can be achieved without harmfully affecting the hepatic functions. Transarterial chemoembolization mixes the effect of avascular necrosis (AVN) with the effect of regional chemotherapy those are under the influence of arterial embolization. By knowing the fact that the metastases of liver cancer and also perfusion indices in hepatocellular carcinoma (HCC) are via hepatic arteries, doctors chose the TACE method for the treatment of liver cancer. On the other hand, in this method, the radiologists can easily convey antitumor remedies via the arteries. Anyway, medium-level HCC is a sensitive stage of the heterogeneous disease that many patients suffer from, so specialists must consider it as a hazardous syndrome. The TACE procedure could be applied just in cases that the liver function of patients is appropriate yet, the patient liver portal vein do not have any problems and the patients do not have ascites disorder. This review is aimed to figure out the evident advantages of TACE especially by a comprehensive view on the medium level HCC. Because of that this treatment method is suggested as a first-line remedy. At last, the future landscape of the initial factors of research in managing HCC disorders have been summarized.

Keywords: Arterial embolization, hepatocellular carcinoma, transarterial chemoembolization

Introduction

Carcinoma is a type of cancer that starts in the cells that make up the skin or the tissue lining the organs, such as the liver, or kidneys. Like other types of cancer, carcinomas are abnormal cells that divide without control. They are able to spread to the other parts of the body, but not always. Transarterial chemoembolization (TACE) is a particular kind of chemoembolization that is used to block the short

blood vessel that supplies oxygenated blood to the liver (known as a hepatic artery) to treat its cancer. The early stages of liver cancer are known as hepatocellular carcinoma (HCC) that grows a multitude of blood vessels.^[1] Somehow, in most patients who suffer from HCC, the symptoms of comorbidity chronic liver disorder can be seen. Chang Y *et al.*^[2] in a comprehensive study by working on the prevention of disease progression with anti-inflammatory therapy in patients with HCV reported that the expansion of the HCC disorder occurs mostly in a damaged liver. According to their reports, approximately all the patients who have a history of misuse of alcohol, inflammation of the liver, or chronic infections and also a type of fatty liver disease like steatohepatitis. Additionally, HCC disorder often

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relapses after initial remedy because of the neoplasm of the liver. Recent developments in imaging techniques useful in diagnosis and treatment help specialists to easily adapt radical therapeutic strategies such as radiofrequency ablation (RFA) and segmentectomy. As cited by Bray F *et al.*^[1] and Chang Y *et al.*^[2] in patients whose curative care is exerted as a primary treatment stage, the disease will recur at a high rate because of intrahepatic metastasis and multifocal tumorigenesis. However, in patients in whom implementation of curative care cannot be done easily, the TACE method could be performed as a main effective remedy for those who suffer from multifocal HCC.

As reported by a lot of researchers, the primary effective method of HCC treatment adopted widely is TACE. Additionally, TACE can be performed in correlation with the diagnosis stage, angiography, and computed tomography (CT). TACE has the potential of being combined with various treatments such as radiation therapy, percutaneous ethanol injection, and radiofrequency catheter ablation. So, it can be mentioned as an interdisciplinary treatment. Embolization is a treatment method that points to blocking the blood supply to tissues by placing an embolus within the bloodstream. However, it can be used for blocking the blood flow to a tumor so that it causes the abnormal cancer cells to die. Transcatheter arterial chemoembolization is approximately a non-invasive therapy method applied in interventional radiology to limit a tumor's blood supply while delivering chemotherapy drugs to the tumor.^[3]

The developed blood vessels receive nearly all of their needed blood from the liver hepatic artery. According to Lanza E *et al.*,^[4] by working on a prospective study of transcatheter arterial chemoembolization for unresectable hepatocellular carcinoma cited that the remained parts of liver tissue gain their required blood from the portal vein. For this reason, doctors by blocking the hepatic artery could interrupt the entire blood supply to the cancer cells without having any effects on the other parts of the liver. The TACE procedure can be applied in cases where the liver function of the patient is appropriate yet the patient's liver portal vein does not have any problems and the patient does not have ascites disorder. On the other hand, when the liver cancer cannot be managed by surgery and also cancer has not metastasized to the main blood vessels of the liver, the TACE method can be applied successfully. For treating tumors of the liver that grow up to 5 cm, the TACE method is offered by the doctors too, but in this condition, the surgical process takes a long time for diminishing these tumors.^[5]

As mentioned by Miyayama *et al.*,^[6] TACE mixes the effect of avascular necrosis (AVN) with the effect of regional chemotherapy those are under the influence of arterial embolization. By knowing the fact that the metastases of liver cancer and also perfusion indices in HCC are via hepatic arteries, doctors choose the TACE method for the treatment of liver cancer. On the other hand, in this method, the radiologists are easily convey antitumor remedies via the arteries [Figure 1]. According to Llovet *et al.*'s^[7] research, about 40% of the patients who suffer from HCC in

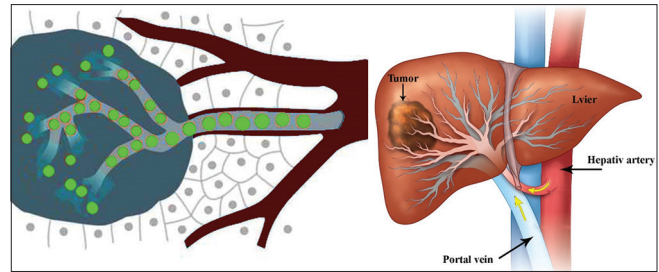


Figure 1: Applying TACE for treating HCC disorder that compounds the effects of ischemic necrosis and regional chemotherapy and also has the advantage of delivering antitumor substances through the arteries. Derived in accordance with^[6]

developed countries are diagnosed initially when the disease has not grown yet. In this early stage, the disease is responsive to remedy methods like ablation therapy, liver transplantation, and segmentectomy.

Anyway, a large number of patients just take conservative and palliative management. Up to now, as cited by Lopez *et al.*,^[8] by working on the analysis of randomized controlled trials on evidence-based management of hepatocellular carcinoma, no comprehensive systemic treatment has been carried out to enhance the survival rate of patients who have progressive HCC. Llovet *et al.*^[9] in a late study reported that the application of sorafenib as a kinase inhibitor drug would be an impressive remedy that may simply improve the treatment outcomes.

Llovet *et al.*^[10] created a classified system for the management of patients who suffer from HCC disorder according to Table 1. According to this classification staging system, TACE is the newest typical method of remedy for patients with HCC disease. As mentioned by some related reports in 2002, the TACE method could extend survival and also easily control the HCC symptoms.^[3,11] When the HCC disorder grows the only effective method for remedy patients is TACE. Given this fact, these patients need such a remedy that is more impressive than the conservative or systemic chemotherapy (chemo). This review presents the discussion of the TACE history and summarizes prior findings of effective techniques for special remedies limited to a local region such as treatment of liver infarction. On the other hand, it is aimed to discuss the application of the TACE method as a helpful drug delivery system for anticancer remedies related to various traumas.

TACE History

The liver circulation is unique among an intricate network of minute blood vessels due to the fact that the blood supply occurs by the hepatic artery and portal vein parallelly. About 80% of the blood supply to the normal liver tissue is delivered by the portal vein. More than 95% of the supplied blood to the cancer cells of the liver is done by the hepatic artery. Transcatheter arterial chemoembolization (TACE) for the treatment of HCC is an adequate method among the patients whose percutaneous ablative or surgical treatments could not be done. According to

Table 1: Classification of the HCC disorder exhibited by Llovet *et al.*^[10]

HCC stage	Preliminary	Early	Intermediate	Advanced	Last stage
Explanation	Child-Pugh A, single HCC<2 cm (PS 0)	Child-Pugh A-B, single HCC, or 3 nodules<3 cm (PS 0)	Child-Pugh A-B, multinodular HCC (PS 0)	Child-Pugh A-B, portal neoplastic invasion, nodal metastases, distant metastases (PS 1-2)	Child-Pugh C (PS>2)

PS: performance status

the results derived from Nakamura *et al.*'s^[12] research, TACE is a treatment technique by injecting embolic agents in the hepatic artery to influence the AVN of liver tumor. Additionally, in 1990, by working on the treatment of hepatocellular carcinoma by segmental hepatic artery, the injection achieved some new outcomes. So, they injected iodized oil into the hepatic artery and resulted that this remedy gradually gathered and retain longly in hypervascular liver tumors.^[13]

Anyway, the TACE method is a treatment for HCC disorder done by vascular and interventional radiology and parallelly requires injection of iodized oil and anticancer remedies in the common hepatic artery.^[12,13] As reported recently by Ueda *et al.*^[14] and Ishikawa *et al.*, the^[15] TACE method is more effective in inhibiting the growth of a tumor than iodized oil or anticancer drugs. Furthermore, in patients who are not appropriate for percutaneous ablation therapy or liver tumor surgery, the TACE method must be carried out.

Explanation and Advantages of TACE

Various agents could have a good influence on the treatment of patients who are affected by the HCC disorder. A lot of these agents are surrogate endpoints of the hepatic reserve, but on the other side, some anatomical factors have been proved to continuously affect the medical prognosis such as detecting the tumor size, the attendance of portal vein invasion, and the number of metastatic tumors. However, the applied anatomical factors are significantly principal for the selection of optimum treatment planning.^[16-18] With reference to the past studies, when the HCC size is more than 5 cm, it is determined as a tumor. In such a condition, the RFA medical procedure cannot effectively treat the disorder because of the tumor size [Table 1].

Tumor multiplicity and its specific conditions in the growth process are when the number of metastasized tumors is higher than three. In such a condition, the success of curative medical care is rare. As cited by Choi *et al.*,^[19] portal venous invasion may be the most remarkable risk factor for instant HCC recurrence after surgical operation. On the other hand, it is a powerful predictive index due to its ability to demonstrate advanced disorders and capability for limiting the number of practical options of treatment. According to Llovet *et al.*,^[10] portal venous invasion is a specific circumstance for TACE. So, for this category of patients only medical palliative care and innovative systemic therapy practicable methods are sufficient.

As reported by Hasegawa, the^[20] TACE method is the most frequent remedy for HCC in such a condition that is not capable

of being surgically removed. Anyway, by applying this method correctly, positive survival outcomes without unfavorable impacts on the functional storage of the liver can be achieved. Traditional TACE is carried out via a chemotherapy injection combined with ethiodized oil also known as Ethiodol and then blockage of a branches of the celiac artery for obstruction the tumor feed. Au and Frenette^[21] by studying the management of hepatocellular carcinoma cited that the HCC disorder made a condition in which the entire blood supply of the liver enhance remarkably from the hepatic artery. It's while in noncancerous liver tumors blockage at the first result in slows tumor development and AVN. The previous developments in the TACE treatment methods included three main aims.

1. Achieving carefully the best remedial method by microcatheterization foundation of branches of peripheral arteries
2. TACE equipped with blocking balloon for increasing survival outcomes
3. Increasing drug delivery by using the drug-eluting beads (DEB-TACE) delivery system

According to studies conducted by Imai *et al.*^[22] on transarterial chemoembolization for hepatocellular carcinoma, some extra methods included are immunotherapy and TACE polytherapy combined with other remedies.

TACE by using the starvation strategy as a treatment tactic induces necrosis of the tumor. This ability of TACE is due to the fact that the hepatocellular carcinomas are fed by the common hepatic artery and also planned for embolization of the distal segment of the common hepatic artery. About 3:1 portion of the blood supply to a normal healthy liver is from the hepatic artery and portal vein. However, while this portion in the patients with cirrhosis of the liver is different, it takes blood flow throughout the two of the mentioned vessels while classical hepatocellular carcinoma tumors take nutritive blood flow only from the hepatic artery. Brown *et al.*^[23] by doing a research around the chemoembolization of the hepatocellular carcinoma recited that embolization is a remedy strategy that by using gelatin sponges, mitomycin C, and/or doxorubicin refers to the lodging of an embolus within the bloodstream. On the other hand, they reported that intra-arterial injection of anticancer remedies with ethiodized oil before the embolic agent stage could mostly enhance the effects of embolism. In addition, as cited by Demachi *et al.*,^[24] the mixture of water within oil-type emulsions could extremely affect the embolization remedy and perception of the tumor. According to Kawamura *et al.*'s^[25] results, compound agents of platinum could have good treatment effects of treatment of HCC disorder and also enhance the resistance

of the TACE method via TACE repetition. Wallace *et al.*^[26] and Kakeda *et al.*^[27] by working on some imaging techniques stated that flat panel detectors (FPD) and cone-beam CT (CBCT) are equipped with the newest imaging technologies that made TACE treatment more precise.

Management and Treatment of HCC

As reported by the national comprehensive cancer network (NCCN),^[28] the TACE method is introduced as a more effective treatment for patients who are affected by intermediate-stage HCC. Lencioni and Crocetti^[29] by working on the local-regional treatment of hepatocellular carcinoma cited that the principle of formal TACE is based on intra-arterial injection of a mild viscous emulsion that is made of chemotherapeutic agents like cytotoxic or anthracycline blended with iodized oil. This mixture is followed by the blood vessel embolization with particles of gelatin sponge or various embolic agents that may increase cytotoxicity by ischemia [Figure 2]. Lencioni *et al.*^[30] had studied transcatheter treatment of hepatocellular carcinoma with Doxorubicin-loaded DC Bead (DEBDOX) and reported that one of the main limitations of conventional transarterial chemoembolization (cTACE) is the instability of the method and its treatment plan. However, due to this limitation, the TACE method could not be accepted as a standard medical oncologic treatment. In spite of the conventional TACE method, the DEB-TACE procedure furnishes repeatability and stability levels. On the other hand, the DEB-TACE procedure performs a more standard and effective technique for the treatment of HCC disorder.

Patients who suffer from HCC disorder are treated by sorafenib as a targeted cancer therapy, for determining if the features of tissue on pretreatment stage computed tomographic (CT) imaging technique could predict general survival. Additionally, sorafenib is the initial systemic operative agent admired by the Food and Drug Administration Federal agency of the United States, in such conditions that HCC disorder is not capable of being surgically removed.^[28] The sorafenib angiogenesis inhibitor

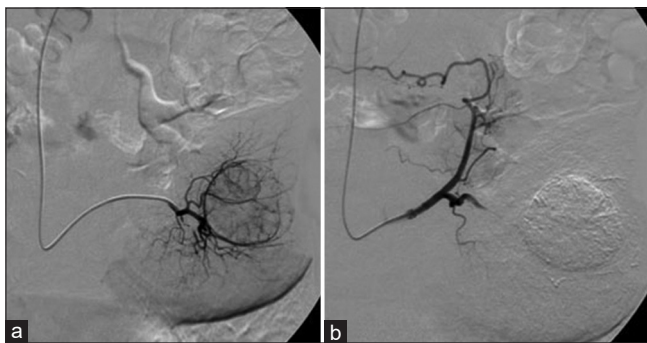


Figure 2: Conventional angiographic image of transarterial chemoembolization. (a) Branches of hepatic arterial that are feeding the tumor with administration of a mixture of anthracycline with oil emulsion followed by particles of gelatin sponge. (b) Angiographic image of the liver after applying the TACE method demonstrates that this method could eliminate tumor vascularity

could reduce the influence of the enhanced growth factor of the endothelium cells of serum vascular that occur after the TACE therapy. This preference provides a methodical motivation for applying an effective mixture of methods for the treatment of such HCCs that are not capable of being surgically removed. For sorafenib administration together with TACE, there are three kinds of procedures:

- It could be performed without interruption all over the designed TACE methods
- Its application may be stopped during any of the designed TACE methods
- It may be approved to be used consecutively after the TACE method.

For integrating clinical data in assessing the proportionality of the TACE method in the treatment of HCC disease, it is compulsory to take magnetic resonance imaging (MRI) or/and CT of the liver. In patients whose HCC disorder is resistant to TACE treatment, the main factors to be taken into account are a reevaluation of the confronting risks of the outcomes of post-exerted TACE. Additionally, as mentioned by Sieghart *et al.*^[31] and Arizumi *et al.*,^[32] this action can be done by using retreatment algorithms like the prementioned TACE retreatment, Child-Pugh, the α -fetoprotein, and the retreatment Response method. Sieghart *et al.*^[31] in a comprehensive study by working on retreatment with transarterial chemoembolization in patients with hepatocellular carcinoma reported that the TACE retreatment result was expanded based on a retrospective study on about 222 patients who were affected by the HCC disorder (according to Table 1 in stage A or B and Child-Pugh A or B) and were treated for two sessions with the TACE method during 90 days.^[33]

Sieghart *et al.*'s^[31] analyses showed that increasing the level of aspartic acid transaminase more than 25%, increasing the score of Child-Pugh, and radiological presence of tumor are the most accurate predictive factors of being survival. So, by referencing their reports, the TACE retreatment rate could be determined easily based on the mentioned factors. By knowing this fact, patients whose TACE retreatment rate before their second TACE session was more than 2.5 were found to not have a long survival rate. Additionally, their outcomes showed that further TACE retreatments could not give major profits to the patients who have the HCC disorder.

There are some conditions that withhold the TACE method to be applied that include a higher level of serum bilirubin, violent abnormality of the liver function as demonstrated by the Child-Pugh score, considerable arteriohepatic deflection of the vein, and disturbed blood flow toward the liver because of the high blood pressure syndrome.^[9] When the number of patients affected by the HCC increased, the rate of contraindications that deny remedy would increase parallelly. For the patients who have advanced-stage hepatocellular carcinoma systemic medical therapy, the anticancer multikinase inhibitor sorafenib is available. Various productive TACE methods are available for treating the HCC disorder with noticeable arteriohepatic venous shunts

that are infrequent disorders that characterize unusual linkages between the branches of the portal vein and systemic veins.

Murata *et al.*^[34] reported that in patients who have the HCC disorder frequently, arteriovenous shunts could be seen in the liver. According to their studies, the HCC disorder attends to the growth within the portal veins and to a minor scope within the hepatic vein, and on the other hand, the involvement of the hepatic, and portal veins make the development of arteriovenous shunts as rare a pathologic condition as possible. As cited by Murata *et al.*,^[34] the main preventive factor in TACE being successful is the attendance of the shunts. Due to this fact, the anticancer remedies or combinations of anticancer remedies and iodized oil quickly pass via them. So, they reported that conventional transarterial chemoembolization (cTACE) is not a beneficial method for HCC disorder in patients who have hepatic arteriovenous shunts, and also, this method may be damaging because of the probability of pulmonary embolism (PE). Where PE is such a condition that blood clots could be stopped within the arteries.

RFA is the procedure of pain reduction and could be an effective remedy in patients with HCCs not bigger than 30 mm. Anyway, almost in all patients, HCCs with arteriohepatic venous shunts are not smaller than 30 mm, and unfortunately, the RFA method could not be performed. Murata *et al.*^[35] in a comprehensive study in terms of temporary occlusion of two hepatic veins for chemoembolization of hepatocellular carcinoma with arteriohepatic vein shunts stated that to dominate the aforementioned restriction, TACE of arteries that feeding tumor should be carried out with balloon obstruction of the correlated hepatic vein that observed via CT and angiography [Figure 3].

Murata *et al.*^[35] introduced a specific effective protocol so that when the location of HCC is in the sidelong portion of the liver, the left hepatic vein should be obstructed with a balloon during the TACE therapy as shown is Figure 4 versus in most of the patients whose objective HCC location is in the middle

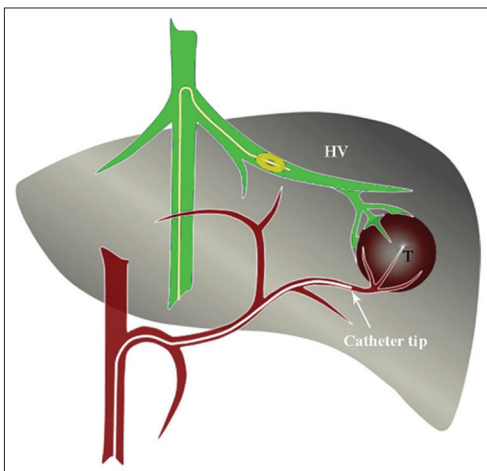


Figure 3: Picture of TACE following hepatic vein blockage for HCC with notable arteriovenous shunts. HV: hepatic vein; T: tumor

or right lobe of the liver (larger lobe of the liver), there is no need to obstruct the hepatic veins with a balloon during the TACE therapy.^[35] In addition, according to the outcomes of Murata *et al.*^[34,35] research by applying the TACE method with the obstruction of correlated hepatic vein via balloon, the growth of tumor could be controlled and also intratumoral shunts of lives eliminated. So, by referencing this improved procedure standard TACE therapy could be carried out for the remaining HCC treatment.

Influences of Treatment on Liver

One of the main conservative regards for HCC treatment in many patients is the strategy of protect function of liver somewhat possible. Ogasawara *et al.*^[36] and Arizumi *et al.*^[37] in various experimental studies reported that critical dysfunction of the liver in cases who were treated with TACE could be seen, mainly in some cases treated with lesser repeated TACE therapies. Ogasawara *et al.*^[36] in a comprehensive survey in terms of the efficacy of sorafenib in intermediate-stage hepatocellular carcinoma patient's refractory to transarterial chemoembolization cited that the period of abnormal function of the liver in patients who suffer from resistant disorders and have treated via TACE therapy was not as long as those patients who changed the TACE therapy to sorafenib.

Additionally, in a similar study by Arizumi *et al.*,^[37] by working on the effectiveness of sorafenib in patients with TACE refractory and intermediate-stage HCC reported that doing repeated TACE therapies in patients who have such a resistant disorder cause an increase in the Child-Pugh score. In patients who changed the TACE therapy to sorafenib, the function of the liver may not decrease as much as in the TACE therapy. Anyway, it could be proved that changing the treatment method from TACE to sorafenib therapy can effectively prevent decreasing dysfunction of the liver. Due to this fact, sorafenib therapy was accepted as an essential treatment method for advanced primary liver cancer.^[38] Raoul *et al.*^[39] demonstrated that in some cases treated with sorafenib, the abnormal function of the liver would be reported. However, the occurrence of this abnormality is not as much as placebo medical treatment comparatively.

Hasegawa^[20] by working on regorafenib second-line systemic therapy tried to develop an effective strategy for changing the treatment method of HCC and by referencing their outcomes reported that monitoring of HCC treatment is an important evaluative step in decision-making for switching TACE to sorafenib-regorafenib ordinal therapy in patients who become resistant to TACE. However, by applying this strategy, sorafenib-regorafenib ordinal therapy could be performed as soon as possible.

Conclusion

Almost half of the patients who are affected by HCC must be chosen for systemic therapy. In this group of patients, the

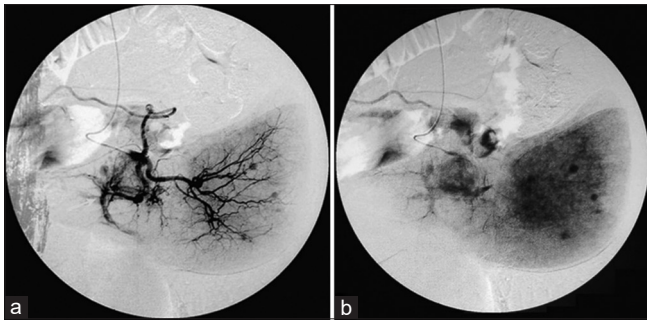


Figure 4: Various HCCs with remarkable arterio-left hepatic vein shunt. (a) Arterial stage; (b) Venous stage. Hepatic angiography demonstrates various HCCs with significant arterio-left hepatic vein shunts (a: arrow)

diagnosing rate is poor and the survival duration of untreated patients is lower than 8 months. TACE, by taking advantage of the dynamics of blood flow in the liver, could enhance a patient's survival. On the other hand, by applying TACE during obstruction of the portal, the survival rate of patients who suffer from advanced-stage HCC will increase remarkably. According to the literature, TACE is the initial recommended treatment of patients with intermediate HCC disorder. Due to this fact, by applying TACE accurately, good survival advantages could be achieved without having any harmful effects on the liver function. Anyway, because of the dissimilarity of the patients who have intermediate HCC disorder, not all the patients would be able to achieve good survival advantages from being initially treated with TACE. Due to the fact that the TACE method is frequently applied to the more extensive groups of patients, a more appropriately designed algorithm for the treatment of patients with the TACE method may enhance the outcomes of the therapy. Combining the TACE method with a heated-up suspension of the anticancer drug will improve that tumor reaction. However, combining ordinary treatments with TACE and anti-angiogenic drugs will prove to be the next recommended future therapy based on TACE.

Having information about the application of a comprehensive corroborated staging system, recognition of the main factors of disease identification, characteristics of patients in treatment method, advantages of treatment, probable hazards of treatment, and also restrictions of treatment method can balance the advantages of being survived versus the risk factors of harmful outcomes.

In some patients who are affected by the intermediate HCC disorder, especially patients whose liver function is normal, more beneficial outcomes will be achieved by applying early aggressive therapies such as surgical or/and ablation therapy approaches. Gao *et al.*^[40] conducted a personalized surgical study on the heterogeneity of the intermediate-stage HCC necessitates and recommended that in patients with stage B HCCs, whose largest size of the tumor is smaller than 7 cm, hematopoietic stem cell transplantation should be applied. The patients whose HCC disorder is at an intermediate level are not recommended for ablation or surgical therapy and their

liver is heavily scarred but can still perform many important bodily functions, TACE method can be applied for treatment as standard therapy. Anyway, in any stages of HCC disorder with unknown tumor bulk size, even when the function of the liver is preserved, the tumor metastasis potential should be evaluated carefully.

In such a condition that the number of metastasized tumors is not so high and one of the tumor dimensions of the largest tumor is greater than 5–6 cm, transarterial radioembolization (TARE) would be recommended. However, if TARE was not accessible or it is detected to not be suitable for the patients, the TACE method would be recommended as appropriate alternative therapy. One of the main options that must be considered is preserving the liver function. So, in any stages of HCCs disorders, it should be taken into account that although the outcomes of remedy are important, the liver dysfunctions must be eliminated without any hazard to other liver organs. As a result, in patients who are affected by the HCC disorder, primary systemic therapy is recommended as an effective alternative method. For instance, patients whose disorder is resistant to the TACE treatment would achieve more advantages with systemic therapies. Some examples of systemic therapy are applying sorafenib combined with a multi-kinase inhibitor like regorafenib in radiological progression cases and treating with sequential therapy strategy via TACE method therapy after applying sorafenib. Although the general effectiveness of these systematic and sequential therapies has not been proved in strict clinical experiments yet, their application is increasing widely.

Additionally, more experimental considerations of measurable indicators are needed to supply a more comprehensive perspective of a patient's therapy method. Due to this fact, for proper usage of the TACE method in patients who suffer from HCC disorders, rational guidelines must be provided for professional clinicians. Finally, a detailed evaluation of the advantages, and disadvantages of the treatment method for any of the patients before applying the TACE method should be considered. For planning the treatment strategy in patients with intermediate HCC, the critical factors to be considered are the selection of adequate treatment for each patient and the selection of the proper treatment time for each patient to achieve more successful outcomes.

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Conflicts of interest

There are no conflicts of interest.

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