

The Combination of TAELE and MWA in the Treatment of Very Large Unresectable HCC: A Case Report

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Abstract

Background: Hepatocellular carcinoma (HCC) is the most common primary malignant tumor of the liver. There are many alternatives of treatment but very limited therapeutic options for unresectable HCC with a single lesion larger than 5 cm. The Interventional Radiology plays an important role with loco-regional treatments. According to BCLC Transcatheter arterial chemoembolization (cTACE) is the standard treatment but the control of large HCC with TACE alone is still a problem and the chemotherapy-related toxicity is frequent.

Case presentation: A 60-years old man with a long history of alcohol abuse was admitted to our Institute for occasional finding of hepatic nodule. The patient was diagnosed with large unresectable HCC; in a multidisciplinary setting it is indicated to perform a cycle of Trans-Arterial Lipiodol Embolization (TAELE), a bland embolization without the use of chemotherapeutic agents. The CT on 40 days showed the persistence of an active residue, so it was performed a new cycle of TAELE combined with Micro-Wave Ablation (MWA). The course was complicated by the formation of a liver abscess treated with placement of percutaneous drainage. Four months after the treatment the control CT shows Lipiodol deposits at the level of the target area and the absence of residues or new hepatic focal lesions.

Conclusions: The combination of loco-regional treatments such as TAELE and MWA is an effective treatment in patients with large unresectable HCC without extra-hepatic disease.

Keywords: HCC; TAELE; MWA

Introduction

Hepatocellular Carcinoma (HCC) is the fifth most common cancer in the world, risk factors include viral hepatitis (hepatitis B and C), alcoholic liver diseases and non-alcoholic steatohepatitis liver diseases. HCC is a morphologically heterogeneous tumor and its origin is believed to be related to repeated cycles of necrosis and regeneration. It is often found in the setting of screening programs for patients with known risk factors; the clinical presentation is variable and depends on the stage of the tumor and background cirrhosis. Treatment options for HCC are dependent on tumor staging and liver function, (updated Barcelona Clinic Liver Cancer classification system). Surgical resection, local treatments and liver transplantation are valid therapeutic options for early/intermediate tumor stages; systemic therapy is recommended for advanced diseases. Despite the variety of treatments, it is very difficult to treat a single unresectable lesion larger than 5 cm (Barcelona Clinic Liver Cancer stage A). According to BCLC cTACE is considered the first-line treatment, but the effectiveness of cTACE alone in the treatment of large HCCs (> 5 cm) is limited. Moreover, because of the side effects it is often poorly tolerated. The combination of loco-regional treatments (thermal ablation and endovascular treatments) using a bland embolization without the use of chemotherapy can represent a valid option of treatment in unresectable HCC without extra-hepatic disease.

Case Presentation

A 60-years-old male patient with a long history of alcohol abuse was admitted to our Institute for the occasional finding of a liver nodule. The multi-phase CTCE showed the presence of a single large hepatic nodule (82x73 mm) at the level of VIIs with contrastographic characteristics typical of HCC and absence of extra-hepatic disease (BCLC A). The patient was clinically evaluated and subjected to blood tests (Child-Pugh A6) and the case was discussed in a multidisciplinary setting in order to evaluate the best therapeutic strategy. According to guidelines the Patient was candidate for surgical resection but, because of the reduced hepatic functional reserve, surgery was at high risk of liver failure; so, it was indicated loco-regional treatment of TAELE. Firstly, in a sterile environment and after local anesthesia, the left femoral access was achieved using a 18 G needle, and a 5F-sheath was inserted via the Seldinger technique. Secondly, the right hepatic artery was selectively catheterized using a 5 Fr C1 catheter; a 2.7 Fr microcatheter was used to super-selectively catheterize the tumor-feeding arterial branches. When the target artery was reached, injection of Ethiodol (4 cc) and PVA particles were carefully injected under fluoroscopy for the embolization of the tumor until blood stasis. The CBCT control confirms the good procedural outcome. Hemostasis of the access site is performed with a dedicated device and manual compression for 5 minutes. After 40 days from TAELE treatment, CT demonstrates Lipiodol deposits in correspondence of the lesion with persistence of an active residue. Therefore, in a multidisciplinary setting it is recommended to perform a new cycle of TAELE combined with MWA. In a sterile environment, after 5-Fr right femoral access, selective catheterization of the right phrenic artery was performed with C1 5 Fr catheter whose arteriography shows multiple collateral branches with a tortuous course that feed the known nodular area at the level of the VIIs, as CT data. Therefore, super selective embolization of the feeder branches was performed using a 2.4 Fr microcatheter with injection of Ethiodol and 45-150 um PVA particles. The CBCT control confirmed the good procedural outcome with contrast deposition in correspondence of the target area. Subsequently, after local

anesthesia and under US-guidance MWA was performed using a MW needle inserted intercostally and treatment was performed for 5 minutes and after retreating by 3 cm, new treatment was performed for 4 minutes with power 150. At the end the application system was removed after track ablation to avoid tumor seeding. No complications are observed. After about 10 days US showed a peri-hepatic fluid layer and CT confirmed a superfluid-aerial peri-hepatic collection (12.5x8.5 cm) and showed right pleural effusion and atelectasis of the LID. Therefore, it was indicated to perform CT-guided percutaneous drainage of the collection. In a sterile environment under CT guidance, after local anesthesia, puncture of the known collection is performed with an 18 G needle and 20 cc of puruloid material was aspirated in order to do bacteriological examination. At the end 8 Fr pig-tail drainage was positioned on the 0.035 guide and fixed with a skin stitch. At the final CT, the known collection appeared small in size without evidence of peri- and post-procedural complications. After one month the CT scan showed the reduction of pleural effusion and the complete detension of the collection. So, the drainage is removed, also in consideration of the improvement of the clinical-laboratory data. The controls CT on 2 and 4 months from the second treatment showed the presence of Lipiodol deposits at the level of VIIs with absence of residues or new liver focal lesions (Figure 1-9).



Figure 1: CT before the treatment, showed a larger lesion (82 x 73 mm) with contrastographic characters of HCC at the level of VIIs.



Figure 2: US (before the treatment) showed a very large lesion at the level of VIIIs.

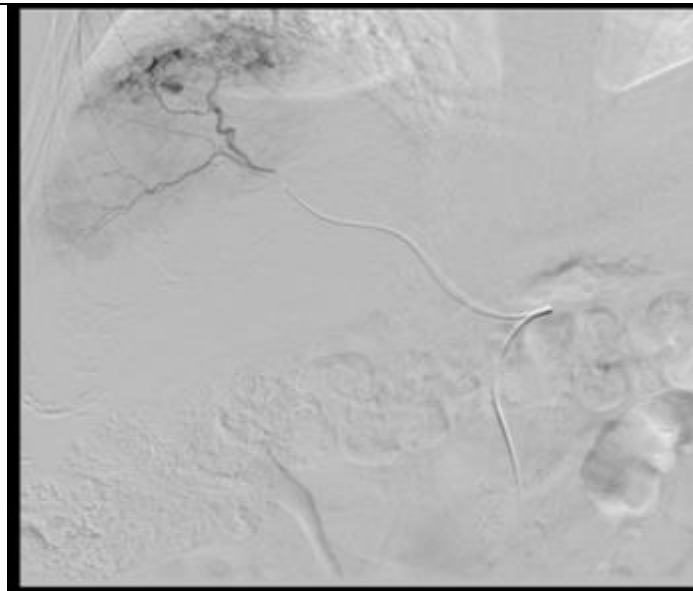


Figure 3: The treatment of Trans-Arterial-Ethanol-Lipiodol-Embolization (TAELE). 3a) Arteriography of right hepatic artery shows multiple collateral branches with a tortuous course that feed the known nodular area at the level of the VIIIs.



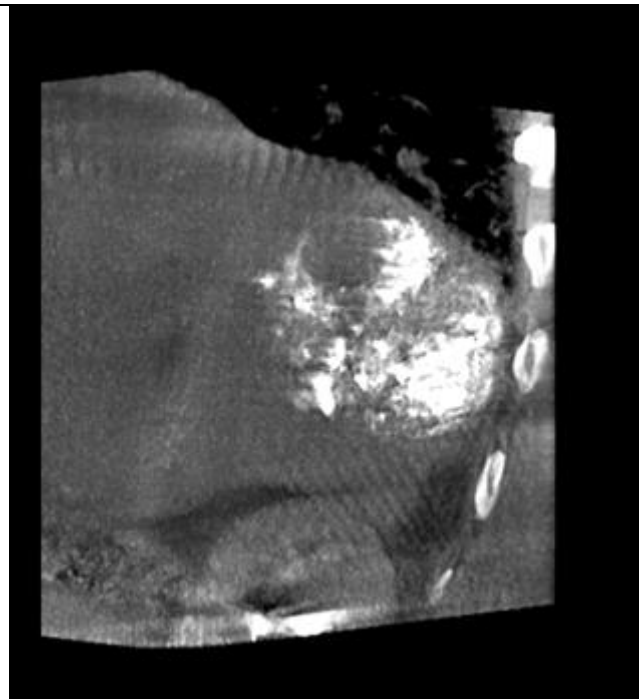
3b) Final CBCT showed deposits of Lipiodol in correspondence of the target area without peri- and post-procedural complications.



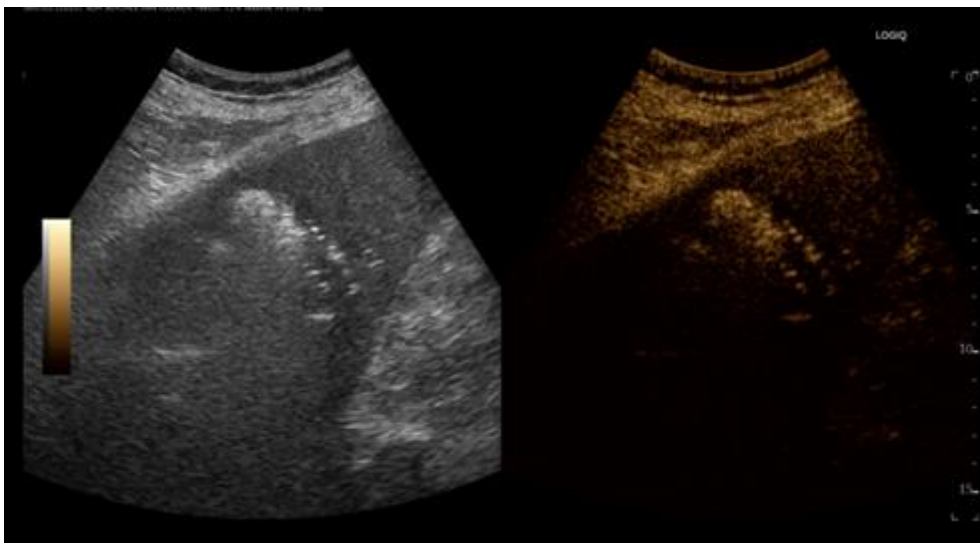
Figure 4: CT (arterial phase) after 40 days from TAELE showed deposits of the Lipiodol at the level of VIIIs and the persistence of an active residue.



Figure 5: The combination of TAELE + MWA. 5a) Arteriography of phrenic artery shows multiple collateral branches with a tortuous course that feed the known nodular area at the level of the VIIs.



5b) Control CBCT showed the good procedural outcome with deposition of Lipiodol in correspondence of the target area.



5c) MWA treatment with CEUS control.

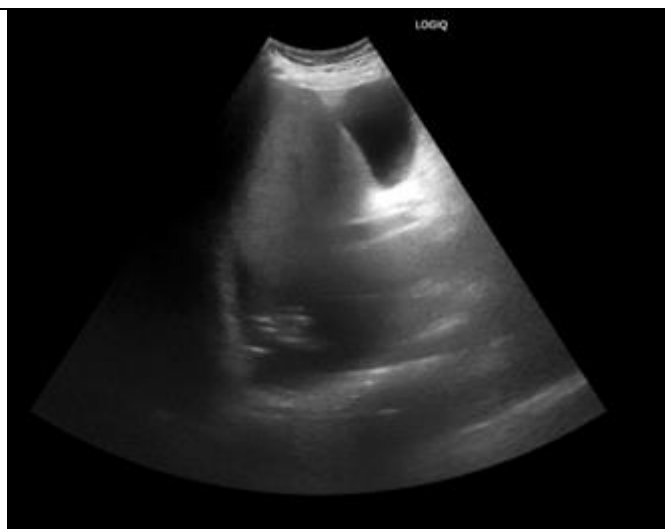
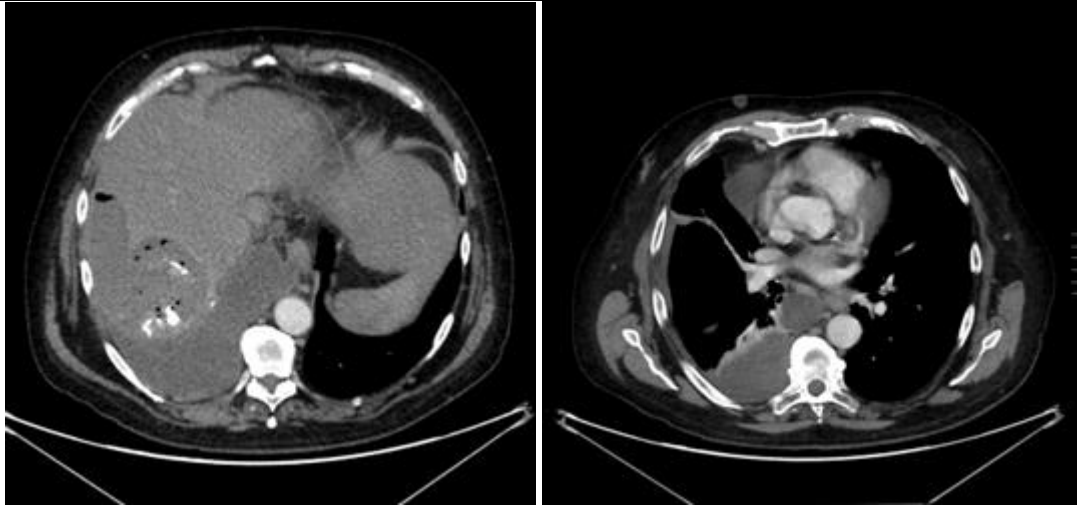


Figure 6: US and TC after about 10 days from treatment. 6a) US showed peri-hepatic collection.



6b) CT confirmed peri-hepatic collection and showed pleural effusion with atelectasis of LID.

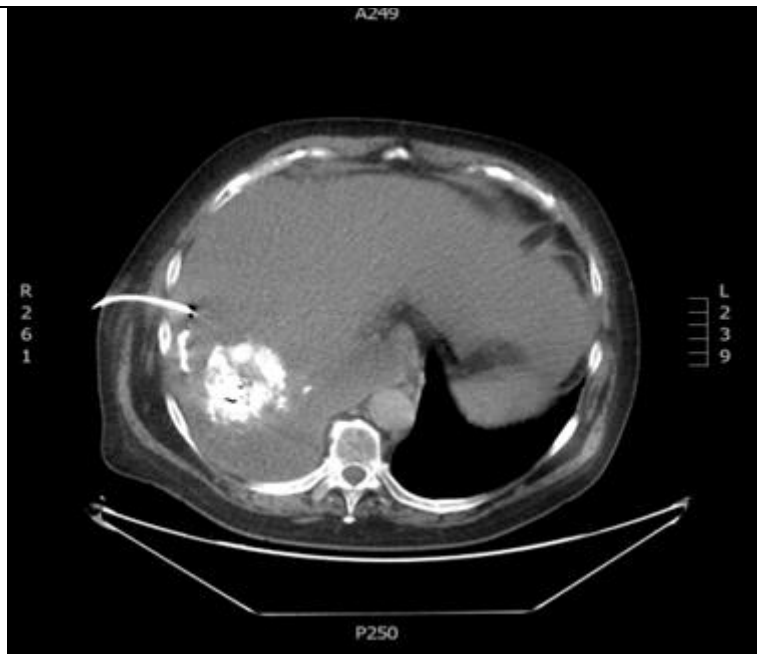


Figure 7: Percutaneous CT-guided drainage.

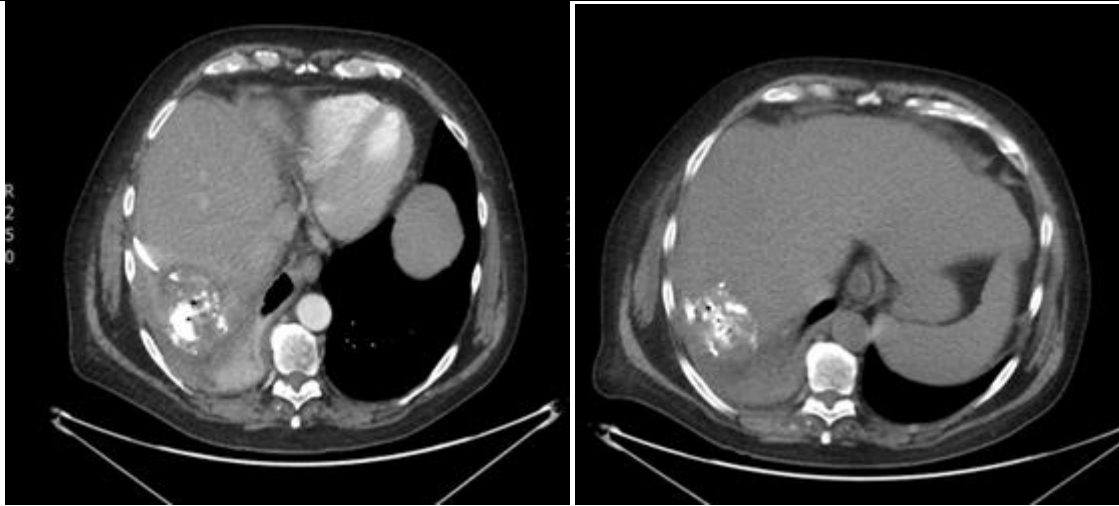


Figure 8: US and CT after 1 month from the placement of percutaneous drainage showed the detention of the collection, so the drainage was removed.

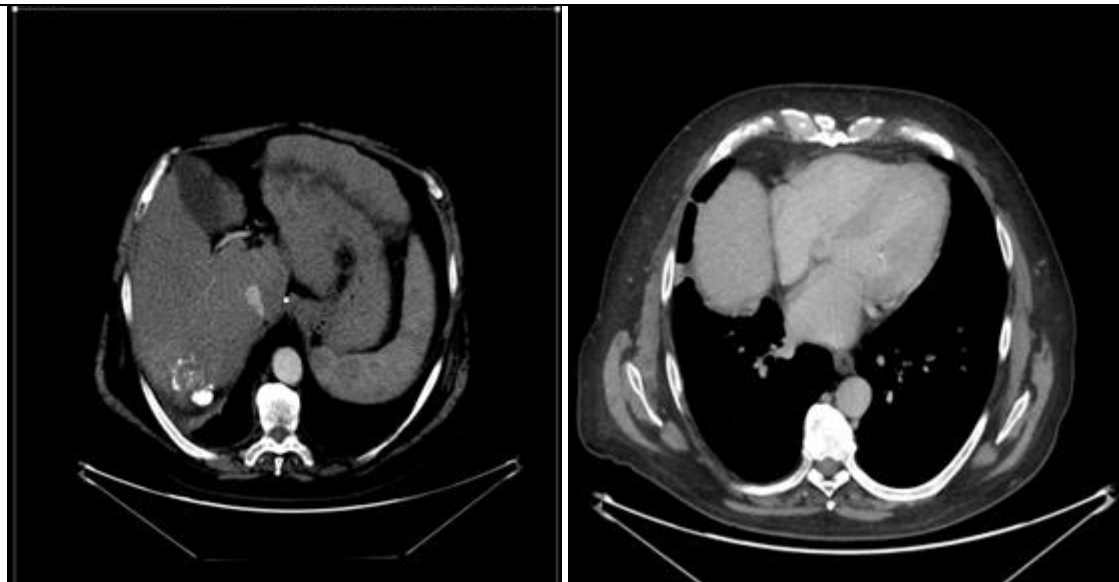


Figure 9: CT after 4 months from the treatment (TAELE + MWA) showed Lipiodol deposits at the level of target area, the absence of residues or new hepatic lesions and the resolution of pleural effusion with atelectasis of LID.

Discussion

Hepatocellular carcinoma is a morphologically heterogeneous tumor with various histological subtypes (fibrolamellar, scirrhous, clear cell type, steatohepatic, macrotrabecular massive, chromophobe, neutrophil-rich, and lymphocyte-rich). The molecular classification distinguishes the proliferative class which includes more aggressive HCCs (chromosomal instability, poor degree of differentiation, frequent vascular invasions and increased AFP levels) and the non-proliferative class which shows less aggressiveness (chromosomal stability, high or medium degree of differentiation, less frequent vascular invasions and low serum levels of AFP). A further molecular classification distinguishes the immune class characterized by high levels of infiltration by inflammation cells and the immune-excluded with a poor T-cell inflammatory infiltrate. Assigning a HCC to an appropriate subtype is important in order to personalize the therapy and improve the prognosis of the patient. The type of the treatment is dependent on tumor

staging and liver function according to the updated BCLC classification system. Surgical resection, loco-regional treatments and liver transplantation are valid therapeutic options for early/intermediate tumor stages. For advanced diseases, systemic therapy is recommended [1]. For the early stage (single nodule, BCLC A) surgical resection is considered the most effective treatments, but hepatic resection is often associated with significant preoperative mortality and morbidity. In these cases, it is compulsory to find alternative treatment, since no extra-hepatic spread is present loco-regional treatments offer valid treatment options. Loco-regional treatments include hyperthymia ablation therapies (RFA and MWA) and endovascular treatments (TACE, TAE and TAELE). Hyperthymia ablation therapies for HCC include Radiofrequency Ablation (RFA) and Microwave Ablation (MWA) [2]. MWA presents some advantages than RFA, it is less affected by the heat sink effect, offers larger ablation area and is faster than RFA [3]. It is especially superior when treating larger tumors [4]. However, thermal ablative treatments are principally performed in patients with small-volume HCCs (≤ 3 cm).

Endovascular therapies include TACE, TAE and TAELE. According to BCLC staging system cTACE is the standard treatment for large unresectable HCC. The embolization of the hepatic artery during TACE reduces the blood flow, creates ischemia and increases the contact time between the chemotherapeutic agent and the tumor cells, resulting in an increased local effect on the neoplasm with only slight damage to the surrounding liver tissue [5]. A recent meta-analysis concluded that there isn't evidence to support or refuse cTACE in patients with unresectable HCC [6]. HCC is a chemoresistant tumor and there isn't a specific chemotherapeutic agent with proven good efficacy. Although cTACE prolongs survival, it is poorly tolerated because of post-embolization syndrome and other severe complications [7-9]. On the other hand, Trans-Arterial Embolization (TAE) is the procedure that leads to the mere occlusion of the arterial flow to lesion through the injection of embolizing agents [10-12] such as PVA particles that can cause a permanent or semipermanent arterial occlusion and achieve a more distal obstruction [13]. The embolization-related ischemia might be the main factor inducing reduction in tumor size which was significantly higher in patients treated with TAE than cTACE [14]. Therefore, many studies demonstrate that TAE is a safe, less toxic and effective treatment for unresectable HCC. But to be really efficient, it is mandatory to embolize all tumour sinusoids and the first venous outflow drainage areas (the portal venous side of the tumour); this can be achieved with TAELE. The TAELE (Trans-arterial Ethanol Lipiodol Embolization) is another endovascular treatment which uses a mixture of lipiodol and ethanol. Ethanol produces an embolization effect by causing endothelial damage and thrombosis of the feeder vessels with a coagulative necrosis of tumor [15]. From the fluoroscopic observation on an animal model, dual embolization could be induced by the slow infusion of an insoluble substance (lipiodol-ethanol mixture), which appears as small droplets passing through the hepatic sinusoids and to the portal vein [10]. The long-lasting embolization of both the arterioles and portal venules is highly effective in causing infarction of the whole tumor including the tumor border, which is commonly supplied by portal venules [16]. In the past, Ethanol has been widely used in the percutaneous approach for small unresectable HCCs [17], proving to be a safe, effective, repeatable and low-cost therapy for HCC, with lower rate of major complications, if compared to other loco-regional treatments. Embolizing procedures using Lipiodol and Ethanol have also been described for HCC by many authors; Park et al. [10] performed this procedure on 14 male patients with single small HCC, Cheng et al. [18] described a similar approach on 20 patients with inoperable tumors, recently Gu [19] proved the effectiveness of trans-arterial embolization of HCC using a mixture 1:1 of Ethanol and Lipiodol, concluding that this procedure could be better than TACE in treating refractory disease. Moreover, Yu et al. [20] in 2009 concluded the superiority of TAELE compared to TACE in a case-controlled study. With regard to the adverse events,

embolization-related symptoms, the elevation in serum levels of transaminases and total bilirubin were more frequent in patients treated with cTACE than TAELE.

TAELE showed to be more effective in tumor devascularization and size-reduction and less toxic than conventional TACE, with similar one-month radiological outcomes according to mRECIST and similar 36-month survival [21]. The efficacy of endovascular treatments is influenced by many factors (blood supply, the size of tumors, and the ultra-selectivity of the catheter) and it is almost impossible to achieve complete killing of the tumor cells. Moreover, patients with tumors greater than 5 cm have a higher prevalence of extracapsular tumor invasion into the liver parenchyma, more frequent intrahepatic dissemination and worse survival rates compare with those with smaller tumors [22]. For these reasons, the control of large lesions with endovascular treatments alone is still a challenging problem [23]. The remaining viable tumor cells may cause local recurrence and distant metastasis [24,25]. Locoregional intraarterial treatments can be combined with other therapies like thermal ablation [26]. Several authors investigated the efficacy of TACE combined with thermal ablation for HCC, such as RFA [27-30] or MWA [31] in unresectable HCC showing a superiority to the monotherapy with TACE or ablation alone. TACE combination with ablative therapies has recently been used to exterminate residual tumor cells after effective TACE treatment [32]. MWA delivered after TACE to treat tumors larger than 5 cm can promote the efficacy of treatment and play a joint role in inhibiting and killing tumors. First, TACE blocks tumor nourishing arteries and further promotes the tumoricidal effect of chemotherapeutic drugs. Second, MWA reaches a large ablation range with its high thermal efficiency and triggers an immune tumoricidal effect secondary to tumor antigen exposure after MWA [33]. Only few studies have evaluated the combination treatment TAE/TAELE and MWA; these studies shows that the combination is associated with better local tumor control and better Overall Survival (OS). The combination therapy may increase the mutual therapeutic effects as follows: local microperfusion of tumors decreases significantly after embolization, reducing the possible perfusion-mediated tissue cooling effect and increasing the ablation range [34]; the deposition of lipiodol after embolization causes stronger heat conduction and tumor local edema, which relatively increases the water content, both increasing the microwave heating rate and enlarging the ablation range [35] and embolization can control microscopic vascular invasion and satellites around the HCC, reducing the local recurrence rate. So, the combination of loco-regional treatments can be a successful and valid option of treatment in unresectable HCC larger 5 cm. Because of advantages of MWA and TAELE, compared to RFA and TACE, TAELE combined with MWA plays an important role. Ischemia and hypoxia may be potent stimulators of angiogenesis and carcinogenesis, which promote collateral circulation and the restoration of tumor blood supply; and these may eventually lead to tumor proliferation and recurrence [36,37]; a valid option can be the association with Bevacizumab, an anti-VEGF monoclonal antibody.

Conclusions

There are many therapeutic options for primary Hepatocellular Carcinoma (HCC), but very limited options for large unresectable HCC with a single lesion larger than 5 cm. (Barcelona Clinic Liver Cancer stage A). Interventional Radiology plays an important role with loco-regional treatments since the absence of extra-hepatic disease. According to guidelines cTACE is the standard treatment, but it is not very effective in large HCC and is poorly tolerated. HCC is a chemoresistant tumor and the embolization is the key point in endovascular treatments. TAELE is more effective in tumor devascularization and size-reduction, and less toxic than conventional TACE. The control of large lesions with endovascular treatments alone is still a problem; TAELE combined with MWA appears to be an effective and promising approach for the treatment of large-sized unresectable HCCs.

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