Interventional Therapies for Hepatocellular Carcinoma

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Introduction. Hepatocellular carcinoma (HCC) is a significant health concern due to its increasing incidence and complex management. Ablation, chemoembolization, and radioembolization are the therapies which are commonly used interventional techniques in treating HCC. Transarterial embolization, transarterial chemoembolization and transarterial radioembolization are widely utilized locoregional therapies for unresectable intermediate and advanced HCCs. This review introduces various interventional therapies which are utilized to treat HCC and highlights new treatment being developed in the immunotherapy agents and combination interventional therapies with immunotherapy.
Keywords. Interventional therapy; Immunotherapy; Hepatocellular carcinoma; Vascular Interventions; Ablation

1. INTRODUCTION

Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related mortality worldwide[1]. Despite ongoing initiatives to curtail the incidence of HCC, projections indicate a further increase in these figures[2]. Multidisciplinary tumour management represents the standard care, with treatment decisions dependent on tumour stage, performance status, and liver function. For those eligible for surgery and falling within the Barcelona Cancer of the Liver Clinic (BCLC) staging system, the standard of care is early resection[3]. In excess of half of HCC patients are diagnosed at an advanced stage (BCLC stage C), thereby rendering them ineligible for treatments[4,5].

Interventional therapies offer alternative options for those patients in whom cannot undergo resection or transplantation. For early- or intermediate-stage HCC (BCLC Stage A or B), interventional therapies including ablation and transarterial chemoembolization (TACE) are available . Radioembolization is reserved for intermediate- to advanced-stage HCC and those with invasive portal vasculature[6].

2. ABLATION

A variety of ablations have been demonstrated to be efficacious in treating hepatic carcinoma lesions that do not conform to the criteria for surgery. To kill the tumor tissues, Radiofrequency ablation (RFA) probes deliver low-voltage alternating current to the lesion[7]. The most apparent benefits of RFA in comparison to surgical intervention are its minimally invasive nature, the lower incidence of complications and the reduced

treatment cost. The evidence regarding the comparative outcomes of RFA and surgery is inconclusive. A study demonstrated that survival rates at 1, 2, and 5 years were inconclusive despite indicating that local recurrence was more prevalent in patients who underwent RFA. Researchers.[7] demonstrated that surgical treatment yielded superior survival rates for individuals with lesions larger than 3 cm. Conversely, for tumors measuring less than 3 cm, the survival rates were comparable between RFA and surgically resected lesions..

Percutaneous injection of absolute ethanol remains viable for treating lesions where RFA is contraindicated for the proximity of vital structures[8]. The ethanol induces coagulative necrosis through dehydrated fixation, which ultimately causes the death of tumour cells. The optimal results were observed in cases where the diameter of the lesion is less than 2 cm[9].

A common ablation method is cryoablation. Tumour tissue is subjected to temperatures of between -20 and -60°C, resulting in damages. One advantage of cryoablation is decreased incidence of injury to the gallbladder or bowel, as well as the reduced level of discomfort experienced by patients with lesions situated in close proximity to the diaphragm[10-12]. It has been demonstrated in studies that, despite the fact that cryoablation does not allow for postablation tract cautery, there is a comparable risk of bleeding when hemostatic agents are used[13]. Furthermore, the rates of survival observed following cryoablation are comparable to those seen after RFA, with 81.4% and 60.3% survival at 1 and 3 years, respectively[14].

Additionally, microwave ablation is an effective treatment for HCC by heating the surrounding tissues, leading to coagulative necrosis and consequently resulting in cell death[15,16]. The efficiency of microwave ablation causes an increased necrosis, an improved state of vascular coagulation and a reduction in ablation times[16]. A comparative analysis of the efficacy of microwave ablation and surgical resection revealed that the survival rates at the 1-, 3-, and 5-year follow-up periods were 91.2%, 72%, and 59.8%, respectively. The 5-year survival rate corresponded with survival with surgical resection[17,18]. Moreover, there is no significant difference in survival or effectiveness between microwave ablation and surgical resection in cases where the lesion is less than 3 cm in size[19,20]. In a comparative analysis of microwave ablation and RFA, the authors[21] evaluated the efficacy of treatment in lesions up to 5 cm in size. A complete response was observed in 86.7% of lesions treated with microwave ablation, in comparison to 83.4% of lesions treated with RFA. However, another study[22] demonstrated that microwave ablation exhibited a significant advantage over RFA, with lower rates of local tumour progression.

Another novel ablation technique in the field of HCC treatment is laser ablation. The electrical energy is transformed into light energy, which then causes the target tissue to heat up and result in cell death[23]. Further research is required in the fields of both laser ablation and HIFU in order to advance the treatment of HCC lesions.

3. VASCULAR INTERVENTIONS

The vascular structure of HCC presents a distinctive treatment paradigm. The majority of HCC lesions are perfused by the hepatic artery, in contrast to the remainder of the healthy liver tissue that is perfused by both the portal vein and the hepatic artery. This offers a distinctive opportunity for transarterial vascular interventions in the treatment of HCC.

Transarterial embolization (TAE) and transarterial chemoembolization (TACE) are two widely used locoregional therapies for unresectable intermediate and advanced HCCs[24]. Although TAE and TACE are regarded as non-curative therapies, they are typically the only options available for patients with advanced HCC when surgery and percutaneous ablation are not feasible. Transarterial radioembolization (TARE) represents an emerging modality that has yielded promising results for intermediate and advanced HCC[25].

3.1. HAIC for HCC

In recent times, treatments for unresectable HCC have undergone a notable evolution. A number of systemic chemotherapy drugs are approved for use and recommended by clinical guidelines across the globe. While systemic treatments are efficacious and can prolong patient survival, their effects are inadequate for macrovascular invasion. Hepatic arterial infusion chemotherapy (HAIC) represents a conventional therapeutic approach for advanced HCC. A worldwide consensus on the recommendation of HAIC has yet to emerge, largely due to the absence of high-quality clinical trials that demonstrate its survival benefits. Nevertheless, there is now a growing body of clinical evidence to support its survival benefit as effective locoregional treatment for advanced HCC. A variety of different HAIC regimens have been documented, including cisplatin monotherapy, cisplatin in combination with 5-fluorouracil (low-dose FP), lipiodol-suspended FP, and an oxaliplatin-based regimen.

HAIC is a locoregional treatment that employs a catheter technique. The catheter enables the consecutive and direct delivery of anti-cancer drugs to HCC lesions within the liver. The benefits of HAIC include the increased local concentration of anti-cancer drugs in the tumour and the reduction of systemic side effects associated with anti-cancer drugs. However, in order to correctly perform HAIC, the implantation of an indwelling catheter and port system is frequently required. In brief, the catheter is inserted into the femoral, subclavian, or axillary arteries. The catheter is indwelling so that the anti-cancer drugs can be properly delivered to the liver.

A review of the guidelines of the American Association for the Study of Liver Diseases, the European Association for the Study of the Liver, and the Asian Pacific Association for the Study of the Liver revealed no description of HAIC treatment. This is due to the lack of sufficient clinical evidence to support the recommendation of HAIC in the guidelines. In a recent study, researchers [26] assessed the efficacy of a low-dose FP regimen in combination with sorafenib, a conventional HAIC approach. The present study did not find a significant additive effect of low-dose FP in combination with sorafenib in patients with HCC. Nevertheless, a significant additive effect was observed in patients with HCC invasion into the portal trunk, as evidenced by subgroup analysis.

While the study did not meet its primary objective, it suggests that low-dose FP in combination with sorafenib may be an effective treatment for a specific subgroup. In a further phase 3 clinical trial conducted by He et al., the FOLFOX HAIC regimen, comprising oxaliplatin, 5-FU and leucovorin in combination with sorafenib, was found to significantly prolong survival in patients with PVTT HCC in comparison to sorafenib monotherapy[27]. This study demonstrated the benefit of HAIC, particularly the FOLFOX regimen, in combination with sorafenib for hepatocellular carcinoma with portal vein tumour thrombus. In general, there is a paucity of evidence from high-quality clinical studies demonstrating the efficacy of HAIC.

A variety of HAIC regimens have been documented for advanced HCC. The anticancer drugs employed in HAIC include doxorubicin, epirubicin, mitomycin, 5-FU, CDDP (including a fine-powder formulation of CDDP), oxaliplatin and leucovorin. Previous reports indicate that monotherapy or combination regimens of 5-FU and platinum-based anticancer drugs, including CDDP and oxaliplatin, are the most commonly reported and appear to be effective. This indicates that these drugs should be regarded as pivotal in the management of advanced HCC with HAIC. The following content present an overview of several representative HAIC regimens for HCC.

3.1.1. CDDP

CDDP is a highly efficacious anticancer drug that has been employed in the management of numerous neoplastic disorders. CDDP has the capacity to form interstrand crosslinks with purine bases in DNA, which impedes the repair of damaged DNA and ultimately results in the destruction of cancer cells through apoptosis. In the context of a HAIC regimen, a dosage of 65 mg/m² of CDDP is administered, at intervals of between one and two months.

3.1.2. Low-dose FP

Low-dose FP represents a standard HAIC regimen for the treatment of HCC. This is theoretically effective due to the dual functionality of CDDP. In addition to its direct anticancer properties, CDDP is a biochemical modulator to 5-FU, thereby enhancing the antitumour effects of the latter. A number of modifications can be made to the regimen. Generally, a course of low-dose FP consists of 10 mg of CDDP for 30 minutes, followed by 250 mg of 5-FU injected continuously for three hours. This is administered on a daily basis for a period of 5 days. In principle, this weekly regimen is repeated two or three times in one cycle of low-dose FP. In 2002, investigators published a report on the therapeutic efficacy of low-dose FP in HCC with PVTT. The objective response rate (ORR) for low-dose FP was 48%. A one-year survival rate of 45% was observed among individuals with PVTT-HCC[28].

3.1.3. High-dose FP

The favourable outcomes associated with the high-dose FP regimen have been documented in Korean studies 29 and 30. The regimen comprises 60 mg/m^2 of cisplatin on day 2 and 500 mg/m^2 of 5-FU on days one to three. The dose of high-dose FP is two to three times that of low-dose FP. The clinical trial conducted by the Korean Liver Cancer Study Group revealed that the high-dose FP regimen demonstrated a superior tumour response in comparison to the low-dose FP regimen.[31]. It should be noted that

the low-dose FP regimen employed differs from that used in Japan. Furthermore, high-dose FP for PVTT-HCC are attractive.

3.1.4. 5-FU arterial infusion plus interferon therapy (FAIT)

A number of publications have examined the efficacy of 5-FU arterial infusion in conjunction with interferon therapy, a treatment modality known as FAIT. In addition to its role in modulating 5-FU biochemically, interferon has also been demonstrated to directly inhibit cell proliferation and angiogenesis.

3.1.5. FOLFOX regimen

A recent trial demonstrated that the FOLFOX HAIC regimen (HAIF), comprising oxaliplatin, 5-FU and leucovorin combined with sorafenib, markedly extended the survival of PVTT-HCC patients in comparison to sorafenib monotherapy[32]. The median survival time for patients receiving HAIF in combination with sorafenib was 13.37 months, compared to 7.13 months for those receiving sorafenib monotherapy. The ORR of patients administered HAIF in combination with sorafenib and those receiving sorafenib monotherapy was 40.8% and 2.46%, respectively. The HAIF regimen has the strongest evidence base of any HAIC regimen, with positive outcomes in managing advanced HCC. The benefit of this regimen is a relatively higher objective response rate with evidence of prolonged survival. Furthermore, the HAIF regimen was conducted without the implantation of a catheter and port system, which may have circumvented some procedural challenges, as outlined in the report. The absence of a catheter and port system necessitates that patients undergoing this therapy remain in a recumbent position during the administration of anticancer drugs. This may prove to be a considerable inconvenience for patients, particularly given that 5-fluorouracil is administered for 2 days in the HAIF regimen.

The clinical evidence in support of the use of HAIC is gradually increasing; however, further clinical evidence is still required in order to strengthen the case for its application. As the evidence of its efficacy increases, HAIC should be acknowledged as a potent and efficacious locoregional treatment for advanced HCC. HAIC may prove to be promising for the locoregional progression of HCC, such as PVTT HCC.

3.2. TACE/TAE/TARE for HCC

The HCC vasculature is supplied by the hepatic artery, not the portal vein. The segmental hepatic arteries are selectively catheterised via retrograde femoral access, and the tumour are visualized by the superselective angiography. Subsequently, various embolic agents may be administered with the objective of obliterating the vascular supply to the tumour and/or delivering pharmaceutical agents or radioisotopes, thereby arresting or decelerating tumour progression.

Liver embolization for HCC is a common intervention in two clinical settings. The first is for large, unresectable HCCs that are unsuitable for surgery. The second is a bridge therapy before resection or liver transplantation. Generally, the optimal candidates for this procedure unresectable lesions that do not present with vascular invasion or extrahepatic spread, and have well-preserved liver function.

The TACE can fill the tumour with a chemotherapeutic agent using a carrier agent. Traditionally, the carrier agent was Lipiodol, which are largely replaced by TACE,

available in different sizes[33-35]. The chemotherapeutic agent requires preventive medication to avoid side effects[36]. Conversely, TAE can achieve superselective vascular embolization by gelatin sponge, Lipiodol, or microparticles with a diameter of 40 μm or less. In contrast to TACE, no drugs are injected during TAE. Furthermore,no survival benefits from the use of chemotherapy in TACE are found compared with TAE.[37].

TACE has long been considered a standard care for HCC subjects undergoing treatment, which is commonly utilized for patients with intermediate stage disease and is shown in numerous studies to confer a significant survival benefit[38,39]. The concomitant administration of chemotherapy and embolization of tumour vessels offers two principal benefits. Firstly, it increases levels of the drug delivered to the lesion. Secondly, it reduces the incidence of systemic chemotherapy side effects. TACE induces marked ischemic tumour necrosis by obstructing tumour-feeding arteries with a chemotherapeutic agent emulsified with Lipiodol and embolic agents. Nevertheless, a considerable proportion of HCCs (50-86%) display evidence of residual viable tumour tissue[40]. In order to adapt and survive within a hypoxic tumour microenvironment, cancer cells express HIF1α. This activates target genes that are involved in proliferation, angiogenesis and EMT, which in turn results in the development of a more aggressive tumour phenotype. It has been demonstrated that hypoxia is essential in the reprogramming of cancer cells to a cancer stem cell phenotype, which represents a significant factor in the maintenance and recurrence of tumours[41].

Conventional TACE (cTACE) entails the administration of lipiodol in conjunction with the selected chemotherapy agent, most frequently doxorubicin or cisplatin. Subsequently, embolization of the same vessel is performed to prevent washout of the chemotherapy and to achieve ischemia of the tumor. The European Association for the Study of the Liver indicate that TACE is the recommended first-line therapy for intermediate Stage B HCC. Llovet and Bruix [39]demonstrated that patients who received TACE exhibited a greater survival rate than those who received only supportive care. TACE was utilised to downstage patients to a stage at which they qualify for a liver transplant.

The advancement of DEB-TACE has emerged as a significant area of investigation within the scientific community. This technology is principally theoretical in basis, predicated on the assumption that more sustained and prolonged releases of chemotherapy might lead to superior treatment outcomes[42]. Furthermore, DEB-TACE can result in a reduced incidence of postembolisation side effects in comparison to cTACE, along with a lower prevalence of hepatic abscesses and a diminished risk of doxorubicin-induced cardiotoxicity[43-46].

The comparative efficacy of cTACE and DEB-TACE is varying across the studies. In a previous study.[47] a noteworthy improvement in response rates was observed among patients with a Child-Pugh score of B and those with bilobar disease who underwent DEB-TACE. Additionally, researchers[46] demonstrated that both DEB-TACE and cTACE exhibited comparable efficacy when directly compared in a randomised controlled trial.

The newer developments in this field include microballoon devices. They are double lumen microcatheters, comprising a balloon that has been moulded in a proximal position to the tip. These devices are available in a variety of small calibres, with a diameter of 1.8 F. The balloon is inflated in order to occlude the vessel in a proximal position to the tip, thereby preventing backflow. Furthermore, the higher pressure distal to the tip may result in enhanced embolization outcomes. Adverse events may occur, including aneurysmal dilation in the inflated balloon area and rupture of the balloon. A paucity of large prospective studies persists, with the result that this is typically used for special cases in many hospitals.

Radioembolization is a transcatheter intra-arterial therapy that employs the use of a radioisotope, yttrium-90(^{90}Y). It is referred to as TARE and ^{90}Y therapy. Microspheres impregnated with ^{90}Y are delivered through the hepatic artery to the tumors with preferential blood flow. While TACE represents the standard treatment for intermediate HCC, TARE is not included in the BCLC staging system guidelines. In contrast, TARE achieves cell death through radiation damage and is therefore considered a brachytherapy without evident embolic effect. The use of 90Y-tagged glass beads in TARE is both safe and effective in unresectable HCC[48-50]. A meta-analysis indicated that TARE is considerably more efficacious than TACE on survival, time to progression, length of hospitalisation, and complication rates for individuals with HCC[51]. Furthermore, TARE may be employed as a conversion treatment for those would otherwise be considered unresectable[52]. Furthermore, in individuals with hepatocellular carcinoma (HCC) and remnant liver unsuitable for upfront surgery, transarterial chemoembolization (TACE) may serve as a surrogate for portal vein embolization, combining hypertrophy and tumor treatment[38].

A study utilising Y-90 in individuals with HCC demonstrated a statistically significant difference in survival between patients classified as Child-Pugh A and those classified as Child-Pugh B [48]. Furthermore, the portal vein thrombosis (PVT) was demonstrated to reduce survival rates following radioembolization. Researchers[49] examined the Y-90 for treating intermediate or advanced HCC, and demonstrated a median time-to-progression of 11 months, with no statistically difference observed between patients with and without PVT. One study[53] compared cTACE with Y-90 in individuals with intermediate HCC. The time to progression was found to be significantly longer in the cohort treated with Y-90. A meta-analysis demonstrated that Y-90 yielded a statistically significant improvement in OS and time-to-progression than TACE.[50].

TARE represents an attractive intra-arterial treatment, exhibiting a powerful anti-tumour effect and minimal post-embolisation syndrome. It is recommended that the doctors need to inform all HCC subjects of the potential benefits of TARE.

Complications of liver embolization include upper quadrant pain, nausea, moderate ileus, fatigue, fever, and transient elevations of aspartate aminotransferase, alanine aminotransferase, and bilirubin levels. The symptoms are typically transient but can be exacerbated by administrating chemotherapy in TACE[33]. Severe complications, including hepatic failure, gastroduodenal ulceration, renal failure, and mortality are

documented in a limited number of cases.

TACE and TAE are two of commonly employed therapeutic modalities for the treatment of HCC. The recent refinement of interventional radiology techniques has permitted enhanced local control, with TARE rapidly establishing itself as an alternative and expanding indications for intra-arterial therapies. Refinements of selection criteria will optimize the role of treatments.

4. COMBINATION THERAPIES

The rationale for combination therapies is the assumption that, regardless of drug or device class and mechanism of action, each agent (when administered as monotherapy) provides some clinical benefit. As all therapies have limited benefits and the inevitability of progression, combination represents the logical subsequent step. It may be assumed that each component of the combination therapy becomes complementary and beneficial in response, duration of response, progression delay and prolongation of OS.

From a therapeutic point of view, interventional radiologists (IRs) employ a range of techniques that can augment the immune system, thereby enhancing the role of immuno-oncology (IO). These include ablative procedures, such as RFA and MWA, as well as embolic techniques, such as chemoembolization and radioembolization. HCC exhibits several intrinsic immune-related characteristics, including chronic inflammation, an immunosuppressive milieu and T cell exhaustion, all of which contribute to disease progression. These features render the tumour an optimal candidate for investigation using combined interventional therapies with IO.[55]. Interventional therapies can enhance the tumour immunogenicity by releasing tumour-associated antigens, which can result in aggravated systemic antitumour immunity related to CD8+ T cells. Inflammatory cytokines released following ablation causes the release of interleukins, heat shock proteins, and tumor necrosis factor-α. It is thought that this has important prognostic effects, with investigators identifying a correlation between survival and immunocyte infiltration in ablated HCC[56].

The current standard of care does not typically include the routine utilisation of ablative technology in conjunction with IO. The combination of these two approaches is, nevertheless, a scientifically sound proposition, although it is still in the investigational phase. The proposition has been advanced that heat-based ablation, in contrast to cryoablation, may influence the T-cell equilibrium in a manner that favours cytotoxic over regulatory lymphocytes[57].

TACE represents the primary management for intermediate-stage HCC[5,58], commonly utilized in advanced HCC, particularly in Asian countries[4,58,59]. Researchers have investigated the potential survival benefit of combining TACE with TKIs in patients with advanced HCC[60,61]. The rationale for combining TACE with ICIs plus anti-VEGF antibody/TKIs in treating HCC is based on the premise that a synergistic anti-tumour role can be achieved through reprogramming the tumour immune microenvironment by TACE, and prohibiting tumour angiogenesis by anti-VEGF antibody/TKIs[62,63]. A target trial emulation study completed by Gao-Jun Teng et al.

[64]showed the impact of all available evidence: treatment with TACE plus ICIs and anti-VEGF antibody/TKIs therapy was associated with significantly better outcomes than ICIs plus anti-VEGF antibody/TKIs alone in advanced HCC patients without prior systemic therapy. This multicenter study supports TACE combined with ICIs and anti-VEGF antibody/TKIs as first-line treatment for advanced HCC. The results demonstrate that the TACE-ICI-VEGF group exhibited a significantly improved median OS. Median PFS was longer in TACE-ICI-VEGF group. In conclusion, the combination of TACE with ICIs plus anti-VEGF antibody/TKIs as a first-line treatment was related to significantly improved OS, PFS, and ORR compared to ICIs plus anti-VEGF antibody/TKIs alone in individuals with advanced HCC.

The present study (CHANCE001) [65]showed that TACE with PD-(L)1 inhibitors plus MTT significantly improved PFS, OS, and ORR in predominantly advanced HCC patients compared to TACE alone. Subgroup analyses demonstrated a general consistency in survival benefits across clinical subgroups. There are rationales for combining TACE with PD-(L)1 inhibitors plus MTT[63,66]. Firstly, TACE induces a hypoxic microenvironment and an increase in the expression of VEGF in residual surviving cancer tissue. It is conceivable that antibodies targeting VEGF or TKIs may hinder the revascularisation and recurrence of the tumour following TACE. Secondly, The liver has cells that suppress the immune system, which may mean tumours are less likely to be attacked[67]. TACE has been demonstrated to release tumour antigens and proinflammatory cytokines, related to a reduction in exhausted effector cells and T regulatory cells[62,63]. Consequently, it is capable of inducing immunogenic cell death and transforming the immunosuppressive "cold tumour" into "hot tumour" by restoring the immune microenvironment, thereby further enhancing the immune response[68-70]. Thirdly, angiogenesis and suppression of anti-tumour immunity are linked. The VEGF directly influences immune cells and facilitate immune evasion, and indirectly influence immunity by increasing vessel permeability[71]. For example, VEGF can cause the formation of an immunosuppressive tumour microenvironment. This is achieved by hindering the maturation and function of dendritic cells and increasing the recruitment of T regulatory cells and myeloid-derived suppressor cells[72]. Inhibition of VEGF can restore anti-tumor activity and enhance the efficacy of immune checkpoint inhibitors[71,72]. In conclusion, compared with TACE monotherapy, TACE with antiPD-(L)1 plus MTT shows significantly better PFS, OS, and ORR for patients with predominantly advanced HCC in a realworld setting, with an acceptable safety. In advance of the publication of the results of the ongoing RCTs, the present study offers compelling evidence in support of this combination therapy in HCC.

5. CONCLUSION

Despite the encouraging outcomes observed with current interventional therapies, the development of newer drugs and treatment techniques, in addition to combined interventional therapies with systemic therapies, may potentially enhance the efficacy of treatment and improve overall survival rates of HCC. In comparison to TACE monotherapy, TACE with antiPD-(L)1 plus MTT shows better PFS, OS, and ORR for

advanced HCC in a realworld setting, with an acceptable safety. Preliminary studies combining conventional interventional therapies with immunotherapies have been particularly promising, and several active trials are anticipated. In conclusion, the results of the new trial will almost certainly contribute to a paradigm shift, definitively improving the current conventional treatment for hepatocellular carcinoma.

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Table1

Programme	Research or paper	Research type	Research objective	End points	Outcomes
Ablation	Chen et al.2010(40 patients)	Retrospective study	Cryoablation	OS(3 years)	60.3%
	Zhang et al.2013(155 patients)	Retrospective study	MWA VS RFE	CR	86.7% vs 83.4%
	Potretzke et al.2016(154 patients)	Retrospective study	MWA VS RFE	PD	8.8% vs 17.7%
HAIC	Young Eun Ahn et al.2020(73 patients)	Retrospective study	HAIC vs sorafenib	OS	10.0 months vs 6.4 month; p=0.139
	Jaejun Lee et al.2021 (244 patients)	Retrospective study	HAIC vs lenvatinib	OS	10.8 months vs 7.9 month; p=0.106
TACE	Lammer et al. 2010(212 patients)	Retrospective study	DEB-TACE vs cTACE	ORR	52% vs. 44%, P<0.05
	Golfieri et al.2014(177 patients)	Retrospective study	DEB-TACE vs cTACE	OS(2 years)	56.8%vs 55.4%,p=0.949

	Mazzaferro et al. 2013(52 patients)	Retrospective study	Y-90	OS	15 months
TARE	Salem et al.2016(179 patients)	Retrospective study	Y-90 vs cTACE	TTP	26.0 months vs 6.8 month; p=0.0012
	Gao-Jun Teng et al. 2022(826 patients)	Retrospective study	TACE plus PD-(L)1 blockades and MTT vs TACE	PFS	9.5 months vs 8.0 month; p=0.002
Combination therapy	Gao-Jun Teng et al. 2024(1244 patients)	Retrospective study	TACE-ICI-VEGF vs ICI-VEGF	OS	22.6 months vs 15.9 month; p<0.0001

MWA, microwave ablation; RFA, radiofrequency ablation; HAIC, hepatic arterial infusion chemotherapy; cTACE, conventional transarterial chemoembolization; DEB- TACE, drug-eluting bead transarterial chemoembolization; HCC, hepatocellular carcinoma; TARE, yttirum-90 transarterial radioembolization; OS, overall survival; CR, complete response; PD, progressive disease; ORR, objective response rate; TTP, time to progression; PFS, progression- free survival.

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