Review Article

Transarterial Therapy: An Evolving Treatment Modality of Hepatocellular Carcinoma

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ABSTRACT

Liver cancer is the fifth most common cancer in men, the seventh most common in women, and the third most common cause of death from cancer worldwide. Only 30-40% of liver cancer patients present early enough to undergo curative treatments such as surgery or liver transplantation. Local treatment with radiofrequency ablation or ethanol injection is often reserved for non-surgical candidates with early stages of disease. Transarterial embolization has become a widely accepted treatment for asymptomatic patients with unresectable lesions. This review discusses in details the three major forms of transarterial therapies: Bland embolization, chemoembolization, and radioembolization.

Key Words: Chemoembolization, embolization, hepatocellular carcinoma, radioembolization, transarterial treatment

Liver cancer or hepatocellular carcinoma (HCC) is the fifth most common cancer in men and the seventh most common cancer in women. The disease-related mortality was estimated to be 649,000 patients worldwide in the year 2008 (477,000 men and 217,000 women). Additionally, HCC is highly fatal, with an overall ratio of mortality to incidence of 0.93.[1] HCC is secondary to liver cirrhosis in 80% of patients, and is the primary cause of death in cirrhotic patients in Europe.[2] Only 30-40% of patients present with early-stage disease open to curative treatments, such as resection or transplantation, while others can only undergo local therapies or palliative care.[2] As a result, liver cancer is the third most common cause of cancer deaths worldwide.[1]

Local ablation with radiofrequency or percutaneous ethanol injection is considered the standard of care for patients with early-stage tumors smaller than 5 cm which are not suitable for surgery. Other newly developed ablative therapies, such as microwave or cryoablation, are still under investigation.

In tumors <2 cm, radiofrequency ablation (RFA) or ethanol techniques achieve complete responses in more than 90% of cases, with good long-term outcome.[3]

Transarterial therapies are recommended for asymptomatic patients with multinodular, unresectable disease stage. In this manuscript, we will be discussing the three major transarterial methods of treatment of HCC: Bland embolization [transarterial embolization (TAE)], chemoembolization, and radioembolization. Transarterial bland embolization (TAE) is done using a catheter inserted into the hepatic artery that injects embolizing agents to block blood flow to the tumor without infusion of chemotherapeutic agents.[4] When chemotherapeutic agents are injected into the artery prior to the infusion of embolizing agents, this is known as transarterial chemoembolization (TACE). Transarterial radioembolization[5] is done using microspheres containing the radioactive isotope Yttrium-90 selectively injected into the feeding artery.

The purpose of this review is to discuss in further details these three transarterial therapies that have been used to treat cases of HCC.

BLAND EMBOLIZATION

Background

Treatment of liver neoplasms by blocking their arterial blood supply was introduced in the 1950s, and this

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concept continues to be the foundation of TAE, or bland embolization, in the treatment of unresectable tumors.[6,7] Since hepatic tumors derive the majority of their blood supply from the hepatic artery, while the noncancerous liver is supplied primarily by the portal vein, TAE is possible. This allows for selective therapy delivery to cancerous cells and protects the noncancerous liver tissue against ischemic necrosis when the arterial supply is occluded.[8,9]

The goal of bland TAE is to kill tumor cells by blocking tumor vascularity without the administration of chemotherapy. Some commonly used embolizing agents include gelatin sponge particles, polyvinyl alcohol particles, and polyacrylamide microspheres.[10-12] According to a systematic review, gelatin sponge is the most commonly used embolic agent, but polyvinyl alcohol is possibly more effective.[13] Even though neither polyvinyl alcohol nor gelfoam has superior survival benefits over the other, considerably less sessions are required if polyvinyl particles are used, as polyvinyl alcohol is more permanent.[14]

Embolization is recommended for asymptomatic multinodular intermediate-stage disease with no vascular invasion or extrahepatic spread. These patients are considered not eligible for locoregional treatments such as radiofrequency or ethanol ablation. Eligible patients usually have Barcelona Clinic Liver Cancer class B disease.[15] It is important that patients have conserved hepatic function and a relatively unobstructed portal vein.[15-18] Contraindications include decompensated cirrhosis, replacement of both lobes with tumor, extrahepatic metastases, a tumor size larger than 10 cm, severely reduced portal vein flow, untreated varices with risk of bleeding, and bile duct occlusion.[13,19]

Clinical evidence

Cheng *et al.*[20] investigated the benefit of pre-liver transplant TAE in treating HCC. Twenty-nine patients were divided into two groups: Group A received bland embolization before the liver transplant and group B only underwent liver transplant. Results of computed tomography (CT) images showed that the bland embolization induced massive tumor necrosis (>85%) in 63.1% of patients in group A. Patients in group A had a better survival of 84% at 5 years than the patients in group B with a survival of 75% at 4 years. The authors concluded that TAE was an effective treatment for HCC before liver transplant.

In a study by Malagari *et al.*[21], seventy-one patients (60% men; 11% women) with documented HCC of 3-10 cm in diameter and who were not eligible for surgery were treated with TACE. The results showed 97.05% survival at 12 months, and 88.2% survival at 30 months. Additionally, Alpha Fetoprotein levels decreased significantly at 1 month post each procedure.

In 2007, Osuga *et al.* investigated the clinical outcomes of TAE using superabsorbent polymer microspheres (SAP-TAE) as an initial therapy for previously untreated HCC unamenable to surgery or ablation.[18] The study's cohort consisted of 59 patients who underwent bland embolization using 100- to 200-μm reconstituted SAP particles (SAP-TAE) as the primary treatment. The patients underwent a total of 121 sessions of SAP-TAE, with one to five sessions per patient. Postembolization syndrome (PES) was minimal after SAP-TAE in all patients, and no major complications were observed. Thirteen patients underwent SAP-TAE only, while the other 46 patients underwent subsequent chemoembolization. The median survival period was 30 months. Overall survival rates at 1- and 2-year intervals were 100% and 83%, respectively. The authors concluded that SAP-TAE was a safe and repeatable therapy for HCC unamenable for surgery or ablation.

In 2008, Maluccio *et al.*[10] reported their findings from a sample of 322 patients with unresectable HCC who were treated with embolization. Selective embolization of arterial vessels feeding the hepatic tumors was performed with spherical embolic particles (40-120 μm) or small (50 μm) polyvinyl alcohol intended to block the terminal vessels. The survival rates of the patients were 66% at 1 year, 46% at 2 years, and 33% at 3 years, while the median survival for the entire sample was 21 months. The authors concluded that bland embolization with small particles to cause terminal vessel blockade of the hepatic artery was an effective treatment method for patients with inoperable HCC.

In a recent study, 53 patients underwent bland embolization for a total of 74 lesions.[17] Results at 1-month, 3- to 6-month, and 6- to 12-month follow-up were 62%, 37%, and 16%, respectively, for patients with stable disease and 35%, 56%, and 51%, respectively, for patients with partial response. Also, 7% of the patients had a complete response, i.e. no evidence of lesions. Twenty of the 53 patients had at least a 1 year of follow-up, with an overall survival rate of 96%.

Bland embolization has been used for recurrent HCC as well. Covey *et al.*[22] reported their results on the use of bland embolization in 45 patients with postoperative HCC tumor recurrence. In their study, 97% of the 45 patients had Okuda stage I disease. The 1-, 2-, and 5-year survival rates were 86%, 74%, and 47%, respectively, while the median overall survival was 46 months. By their last follow-up, 6.6% of the patients were alive with no evidence of viable disease. The authors concluded that bland arterial embolization following HCC recurrence was an effective method of salvage therapy for those patients with good liver function.

Complications

The most common toxicity from bland embolization therapy and chemoembolization is a PES consisting of fever, nausea,

abdominal pain, and vomiting.[18,23,24] Rare but extreme complications include ischemic hepatitis, pancreatitis, bacteremia, renal failure, and hepatic failure, all of which can lead to death.[17,24-26] Results of several researches using multiple microsphere sizes have shown that though microspheres smaller than 40 mm tend to collect in tumor arterioles, they may pass through arteriovenous shunts and sinusoids into the systemic circulation and, as a result, can cause grave embolic complications.[27,28]

CHEMOEMBOLIZATION

According to the Society of Interventional Radiology,[5] chemoembolization is a minimally invasive treatment for liver cancer that delivers a high dose of cancer-killing drug (chemotherapy) directly to the liver while depriving the tumor of its blood supply by blocking, or embolizing, the arteries feeding the tumor. A Japanese radiologist Dr. Yamada first introduced this technique in the late 1970s for patients with unresectable HCC.[29]

No standard protocol of TACE has been universally adopted, so there are variations in the procedure done and the drugs used. Anticancer drugs used include doxorubicin,[26] cisplatin,[23] and epirubicin.[30] According to the evidence so far, none of these drugs has been proven to be superior to the others.[13,31]

Regardless of the chemotherapeutic drug used, it is usually emulsified in lipiodol, or iodized poppy seed oil, that is used as a carrier for local cytotoxic chemotherapy. When lipiodol is injected into the hepatic artery, it remains in the tumor tissue even after it is cleared from normal hepatic tissue, seemingly due to the absence of Kupffer cells in the tumor.[32] Although previously having been thought to increase the effectiveness of TACE, recent evidence shows that there is no benefit with lipiodol.[13] The embolizing agents used are usually gelatin sponge particles and polyvinyl alcohol.[13]

There is no uniform agreement on the criteria for selecting patients appropriate for TACE. The indications are quite similar to those of bland embolization. Patients with tumor unamenable to surgical resection or ablation, as well as patients with Barcelona Clinic Liver Cancer class B or intermediate-stage disease are usually considered eligible for chemoembolization.[15] The contraindications for TACE are also similar to those of bland embolization, and include decompensated cirrhosis, replacement of both lobes with tumor, extrahepatic metastases, a tumor size larger than 10 cm, severely reduced portal vein flow, untreated varices with risk of bleeding, and bile duct occlusion.[13,19] High albumin level is associated with a better survival, whereas a high alpha-fetoprotein (AFP) level and large tumor size indicate high risk of morbidity.[33,34]

Clinical evidence

Lo et al.[23] conducted a randomized controlled trial (RCT) with 80 patients and reported their findings on a group of patients with unresectable HCC who underwent either supportive care or chemoembolization (given variable doses of an emulsion of cisplatin in lipiodol and gelatin sponge particles). Each patient in the chemoembolization group received 1-15 sessions, with a median of 4.5 sessions per patient. Chemoembolization resulted in a marked tumor response, and the survival rates were considerably improved in the chemoembolization group with 1-, 2-, and 3- year survival rates of 57%, 31%, and 26%, respectively. Survival in the control group was 32% at 1 year, 11% at 2 years, and 3% at 3 years. Another trial by Llovet et al.[26] reported the findings on 112 HCC patients treated with embolization or chemoembolization or supportive care alone. Twenty-five of 37 patients who were treated with embolization, 21 of 40 patients treated with chemoembolization, and 25 of 35 given supportive care died. The 1- and 2-year survival rates were 82% and 63% for the chemoembolization group, 75% and 50% for the bland embolization group, and 63% and 27% for the supportive care group, respectively. The authors of both studies concluded that chemoembolization greatly improves survival of selected patients with unresectable HCC.

In 2006, Takayasu et al.[34] conducted a study on a large cohort of 8510 HCC patients to elucidate the survival of these patients and to analyze the factors affecting the survival. The patients were treated with TACE consisting of lipiodol, chemotherapy, and gelatin sponge particles. Exclusion criteria were any previous treatment taken prior to the TACE and/or extrahepatic metastases. The overall median survival of the patients was 34 months. The survival rates were 82% at 1 year, 47% at 3 years, 26% at 5 years, and 16% at 7 years. According to the authors, the degrees of liver damage, tumor node metastases stage (proposed by the Liver Cancer Study Group of Japan), and the AFP levels were independent risk factors for patient survival. The procedure-related mortality rate after the initial therapy was 0.5%.

An RCT was conducted on 108 patients with resectable HCC to evaluate the effects of preoperative TACE on resectable HCC.[35] The patients were randomly divided into two groups. One group underwent preoperative chemoembolization and the other did not. Five patients in the preoperative chemoembolization group did not undergo surgery because of liver failure or extrahepatic metastasis. The preoperative chemoembolization group had a longer operation time and a lower resection rate. According to the results, there was no considerable difference between the two groups in operative blood loss, surgical morbidity, and hospital mortality. At a median follow-up of 57 months, 78.8% of the patients in the preoperative chemoembolization group

and 91.1% of the patients in the control group had recurrent disease. The overall survival rates for the preoperative chemoembolization group were 73.1% at 1 year, 40.4% at 3 years, and 30.7% at 5 years, while the overall survival rates of the control group were 69.6% at 1 year, 32.1% at 3 years, and 21.1% at 5 years. The authors concluded that preoperative chemoembolization did not improve the surgical outcome because it resulted in drop-out from definitive surgery due to progression of disease and liver failure.

A more recent RCT has shown the effects of a novel chemoembolization procedure on HCC using iodized oil and degradable starch microspheres (DSM).[36] The researchers randomly divided 45 patients with HCC into three equal groups: One group received lipiodol, second group received DSM, and the third one received both lipiodol and DSM. All patients received cisplatin as the chemotherapeutic drug. The response rates were 40% in the lipiodol group, 53.4% in the DSM group, and 80% in the lipiodol + DSM group. The median progression-free survival time for the lipiodol group, DSM group, and the lipiodol + DSM group was 177 days, 287 days, and 377 days, respectively. There were no severe adverse effects amongst the three groups. The authors concluded that transarterial infusion using lipiodol and DSM was superior to transarterial infusion using lipiodol only or DSM only.

Chemoembolization has been compared to other procedures as well. Liem *et al.* reported their findings of TACE applied to 114 patients who were also eligible for RFA.[33] The treatment-related mortality and morbidity were 1% and 19%, respectively, while the overall survival rates at 1, 3, and 5 years were 80%, 43%, and 23%, respectively. The authors concluded that the morbidity, mortality, and survival data after TACE for small HCCs eligible for RFA were comparable to those reported after RFA in the literature, and suggested the need for a randomized comparison of the two treatment modalities for small HCCs. Another study was done to determine the effect of combining chemoembolization with RFA in patients with large hepatic tumors.[20] Patients treated with TACE-RFA had better overall survival rates than those treated with TACE alone or RFA alone. The authors ended by stating that TACE-RFA was superior to TACE alone or RFA alone in improving the survival for patients with HCC larger than 3 cm.

The conclusion of a meta-analysis of seven RCTs evaluating arterial embolization in 545 patients with intermediate unresectable disease gave stronger evidence and showed improved 2-year survival after chemoembolization with cisplatin and doxorubicin compared to controls, with no survival benefit from bland embolization only.[37]

A more recent meta-analysis of nine RCTs has confirmed that TACE does improve survival, and a meta-analysis of three RCTs including 412 patients comparing chemoembolization versus bland embolization alone demonstrated no survival difference.[13]

Based on the aforementioned evidence, TACE has become the standard treatment for unresectable asymptomatic HCC and bland embolization is currently not recommended as a standard first-line treatment for asymptomatic unresectable HCC according to the guidelines of the European Association for the Study of Liver (EASL) and the American Association for the Study of Liver Diseases (AASLD), as well as the Saudi Association for the Study of Liver Diseases and Transplantation (SASLT).[3,38,39]

Although transarterial administration of chemotherapeutic agents helps escaping the first-pass metabolism in the liver and results in delivery of higher concentrations into the tumor, a significant proportion of the dose passes into the systemic circulation contributing to the PES.[40,41] PES occurs in approximately 60-80% of patients due to embolization of the non-involved liver tissue as well as the systemic effect of the infused chemotherapy,[13] and ranges between mild symptoms such as abdominal pain, fever, nausea, and vomiting to life-threatening conditions such as liver failure and abscess formation. In addition to PES, systemic toxicity induced by doxorubicin, such as bone marrow suppression, myocardial dysfunction, mucositis, and alopecia, are commonly encountered in as high as 60% of patients and may limit the total dose administered to a given patient.[13] According to a systematic review, treatment-related mortality was 2.4% (range 0-9.5%) in 37 trials involving 2858 patients.[13]

TACE with drug-eluting beads

Drug-eluting beads (DEB) are soft, deformable, spherical particles composed of a polyvinyl alcohol hydrogel designed to bind with anthracycline drugs such as doxorubicin.[42] More than 98% of the doxorubicin dose is absorbed by the beads after 20-120 min (from 100-300 to 700-900 μm, respectively) of mixing with 25 mg/ml of doxorubicin. Upon loading with doxorubicin, the beads undergo a slight decrease in size, up to 20% when loading at 25 mg/ml, which is more pronounced with larger beads.[43] When beads are infused intra-arterially, elution occurs in a controlled and sustained fashion due to ion exchange with the surrounding environment, unlike the rapid release of the drug from lipiodol in conventional TACE.[42,43] The C_{max} plasma concentration following intra-arterial infusion of DEB loaded with doxorubicin is reached in 5 minutes and is similar for both low and high loading doses.[44] Studies comparing DEB-TACE to conventional TACE pharmacokinetics show that peak plasma concentration of doxorubicin following intra-arterial administration is markedly lower in DEB groups,[44-46] with much slower release of drug into the tumor for a period of more than 14 days.[42]

The clinical introduction of chemoembolization with DEB allowed maximum and prolonged intratumoral release of the chemotherapeutic agent with minimal systemic effects, in addition to tumor ischemia induced by blocking the tumor vascularity.[44,47-49]

Initial phase I/II evaluation of this method conducted by Poon *et al.* revealed no dose-limiting toxicity for up to 150 mg of doxorubicin, which was used for 20 patients in the phase II study.[44] This study prompted other investigators to further evaluate the safety and effectiveness of this treatment. Several RCTs and cohort studies compared the safety and efficacy of c-TACE to DEB-TACE.[45,47,50-56] In the PRECISION V study, 212 patients were randomized to TACE with DCB loaded with doxorubicin or c-TACE with doxorubicin, and the primary endpoint was tumor response based on the EASL at 6 months. Although DEB-TACE group showed higher rates of complete response, objective response, and disease control compared with the c-TACE group, the hypothesis of superiority was not met. However, patients with a more advanced disease showed a significant increase in objective response with DEB compared to c-TACE. DC bead was associated with improved tolerability, with a significant reduction in serious liver toxicity.[47] Ferrer Puchol *et al.* evaluated 72 patients with unresectable HCC (c-TACE $n = 25$; DEB-TACE $n = 47$) and found that the latter method is safe and better tolerated, and may lead to better tumor necrosis. However, there was no statistically significant survival benefit or response rate according to the Response Evaluation Criteria in Solid Tumors (RECIST).[51] A phase II trial comparing 35 patients treated with DEB-TACE to 70 historical controls treated with c-TACE confirmed the previous findings of decreased systemic toxicity and hospital stay.[53] Similarly, a phase II trial randomized 30 patients to either c-TACE or DEB-TACE with superabsorbent polymer (SAP).[45] This study reached the same conclusion of decreased systemic levels of doxorubicin leading to lower incidence of drug-induced toxicity. In a retrospective study of 71 patients, survival in Child–Pugh A and B classes from the first transcatheter therapy was better in patients treated with DEB compared to c-TACE (641 vs. 323 days, respectively). However, there were no significant differences in the median survival of patients in Child–Pugh class C when treated with either therapy.[50]

The administered beads and doxorubicin dose may vary according to the disease volume and distribution. Majority of previous studies used beads with size range between 100-300 and 300-500 μm. Martin *et al.* evaluated[57] 118 patients who received a total of 186 treatments with a median total treatment dose of 75 mg and median overall total hepatic exposure of 150 mg. Most patients were treated with bead sizes of 100-300 μm or 300-500 μm. They reported even distribution of adverse events across bead sizes as well as multiple patients receiving two different bead sizes in one treatment.

The data from a prospective, non-controlled, repeat treatment registry of 206 patients undergoing 343 treatments for HCC indicated that smaller beads offer the opportunity for repeated treatments, a larger cumulative dose delivery, a lesser degree of complete stasis, and fewer adverse events.[58] The recommended treatment dose range reported by the PRECISION study[47] is 100-150 mg per patient, which was shown to be safe and effective even at the highest dose.[46] Dose adjustments for bilirubin levels may also be used, as in Varela *et al.*'s study (<25.6 mol/l, 75 mg/m^2; 25.6-51.3 mol/l, 50 mg/m^2; and 51.3-85.5 mol/l, 25 mg/m^2).[46] The majority of previous studies reported no dose-limiting systemic toxicity effects such as marrow suppression or cardiac failure. In a study comparing DEB-TACE to c-TACE, analysis of the systemic side effects of doxorubicin (alopecia, skin discoloration, mucositis, and marrow suppression) established a significant benefit in favor of DC bead (11.8%) over cTACE (25.9%). Alopecia, the most commonly occurring event, was mild (grade 1) and seen in only one case (1.1%) of DEB-TACE, while in the c-TACE arm, almost half of the alopecia events (11 events) were of pronounced/total hair loss (grade 2). Marrow suppression and mucositis were more common and of greater severity in c-TACE compared to DEB-TACE patients.[47] Reyes *et al.* prospectively evaluated the safety of DEB-TACE in 20 patients with unresectable HCC and found a lower rate of grade 3 and 4 toxicity. Only one patient suffered grade III leukocytopenia 30 days post procedure and six more patients had grade I/II leukocytopenia. Mild alopecia was seen in only one case.[59] The lower incidence of systemic toxicity allows the use of higher doxorubicin dosage, which seems not to be associated with a higher incidence of major chemotherapy-related adverse events.[60] The feasibility of higher dose administration may also enhance the therapeutic response by overriding the capacity of the multidrug resistance pump that characterizes HCC cells.[60]

RADIOEMBOLIZATION

Background
The principle of radioembolization is similar to that of chemoembolization, but it is performed using radioactive microspheres to kill tumor cells instead of cytotoxic drugs. This treatment integrates the radioactive isotope Yttrium-90 into the embolic molecules that are injected through a catheter into the hepatic arteries supplying the neoplasm. The particles block the small tumor blood vessels where they locally irradiate the surrounding cells resulting in cell death.[5] This technique allows for a higher dose of radiation to be administered to a local area, without subjecting a large volume of healthy tissue in the body to

the radiation. Two radioembolic agents are commercially available: TheraSpheres® (Nordion, Ottawa, Canada)[61] and SIR-Spheres® (Sirtex Med ical Inc., Woburn, MA, USA).[62]

External beam irradiation is not effective in the treatment of HCC because of the radiosensitive nature of normal liver tissue.[63] The external radiation doses in excess of 35 Gy will result in liver failure with subsequent ascites, hepatomegaly, and elevated liver enzymes, which will occur weeks to months after therapy.[63-65] With radioembolization, radiation doses of up to 150 Gy can be administered without causing the clinical complications seen with external beam radiation.[66-69]

The criteria for selecting patients suitable for radioembolization have been laid out by a consensus panel consisting of professionals from interventional radiology, nuclear medicine, radiation oncology, medical and surgical fields.[70] Patients who are not amenable to resection or conventional TACE and have a life expectancy longer than 3 months are considered for radioembolization. Contraindications include irreversible total serum bilirubin greater than 2 mg/dl, excessive tumor size with poor hepatic function, and a compromised portal vein.

Clinical evidence

Salem *et al.*[71] carried out a study to determine the safety, tumor response, and survival of 43 patients with inoperable HCC who were treated with Yttrium-90 during a 4-year period. Patients were divided into three groups based on treatment method and risk stratification (group 0, segmental; group 1, lobar low risk; group 2, lobar high risk). Forty-seven percent of the patients had an objective tumor response and 79% had a tumor response when percent reduction and/or tumor necrosis were used as a measure of tumor response. The median survival for group 0 was 46.5 months, for group 1 was 16.9 months, and for group 2 was 11.1 months. The authors reported no life-threatening adverse events related to treatment.

Sangro *et al.*[72] reported their findings on 24 Child–Pugh class A patients with HCC who underwent Yttrium-90 radioembolization. Reduction in the size of target lesions was observed in all but one patient. When taking only target lesions into consideration, disease control rate and response rate were 100% and 23.8%, respectively. The authors concluded that radioembolization using resin microspheres had a significant antitumor effect against HCC.

In 2006, Kulik *et al.*[73] reported their results on 35 patients who were not eligible for transplantation, resection, or ablation, and underwent radioembolization. Sixty-six percent of the cohort was effectively downstaged to resection, transplantation, or RFA. The 1-, 2-, and 3-year survival rates were 84%, 54%, and 27%, respectively, and the median survival by Kaplan–Meier analysis for the entire cohort was 800 days. According to the authors, the data suggested that intra-arterial Yttrium-90 microspheres can be used as a bridge to transplantation, surgical resection, or RFA.

In 2011, Salem *et al.*[74] compared the effectiveness of radioembolization to chemoembolization. Patients with HCC treated by chemoembolization or radioembolization with Yttrium-90 microspheres had similar survival times, but radioembolization resulted in longer time to progression and produced less toxicity than chemoembolization.

In a retrospective study comparing the outcomes between radioembolization and chemoembolization, there was no significant difference in survival. However, PES was significantly more severe in patients who underwent chemoembolization.[75]

A systemic review by Sangro *et al.*[76] concluded that radioembolization has a significant antitumor effect against HCC and can prevent local tumor growth. The authors also said that by implementing strict selection criteria and conservative models for calculating radiation activity that should be delivered, radioembolization can be performed safely even in cirrhotic patients, and without significant PES or radiation-induced liver disease. This is comparable with another recent systemic review by Yang *et al.*,[77] according to which radioembolization with Yttrium-90 microspheres is an effective and safe treatment for patients with unresectable HCC.

Complications

As with bland embolization and chemoembolization, the most common side effect of radioembolization is PES consisting of nausea, vomiting, fever, and abdominal pain.[77,78] Other complications include portal vein thrombosis, jaundice, radiation gastritis, increasing bilirubin level, cirrhosis, and ascites.[77] Table 1 compares the results of different transarterial therapies for HCC.

Table 1: A comparison of different transarterial HCC therapies	
Modality	**Outcome**
TAE vs. TACE	1- and 2-year survival rates: 75% and 50%, respectively, for TAE, 82% and 63%, respectively, for TACE[26] 3-year survival rates: 33% for TAE[10] and 47% for TACE[34]
TACE vs. TACE-DEB	Similar efficacy, but significantly reduced toxicity with TACE-DEB[45-47,50,51,57,60]
TACE vs. TARE	Similar survival rates, but less toxicity with TARE[74,75]

TAE: Transarterial embolization, TACE: Transarterial chemoembolization, TACE-DEB: Transarterial chemoembolization with drug-eluting beads, TARE: Transarterial radioembolization

CONCLUSION

Overall, the evidence today suggests that transarterial therapies of bland embolization, chemoembolization, and radioembolization are effective in the treatment of inoperable HCC, especially if the patients are carefully selected. These treatments have some complications, but have rarely caused any severe adverse effects and, thus, are safe if done correctly. However, there is a need for more evidence to compare these methods head to head, as well as with other treatments of HCC. One of the problems with the current evidences which should be addressed is that the methods of applying the treatments are not standardized among the studies, particularly concerning chemoembolization. More studies should also be done to observe the effects of combining these treatments with others.

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