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Chemoembolization and Radioembolization for Hepatocellular Carcinoma

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Abstract

Hepatocellular carcinoma (HCC) continues to represent a major worldwide problem. While treatments such as resection, transplantation and ablation may provide a chance for cure, these options are often precluded because of advanced disease presentation. Palliative treatments include transarterial embolization and systemic therapies. This review will summarize the state of the science for embolic therapies in HCC (conventional and drug-eluting chemoembolization, radioembolization), as well as discuss related topics including HCC staging, assessment of response and ongoing clinical trials.

Keywords

hepatocellular carcinoma; chemoembolization; radioembolization

INTRODUCTION

Hepatocellular carcinoma (HCC) is the 6th most common malignancy diagnosed worldwide.[1] Its incidence is on the rise and has now become the 3rd most common cause of cancer-related mortality.[2] Late stage presentation, co-morbidities, and limited donor availability enables only 10% of patients to receive curative therapies.[3] According to the Barcelona Clinic Liver Cancer (BCLC) staging system, conventional chemoembolization (cTACE) represents the mainstay of treatment for intermediate BCLC B disease. This has now evolved into more controlled delivery of chemotherapy in the form of drug-eluting bead TACE (DEB-TACE). Radioembolization, also an intra-arterial treatment, represents an alternate form of treatment for HCC patients with BCLC B disease. Rather than injecting chemotherapy, micron-sized non-embolic radioactive particles are injected in the hepatic artery. Studies have shown that radioembolization may also have a role in the treatment of patients with early (BCLC A) or advanced stage disease (BCLC C). This review article will focus on cTACE, DEB-TACE and radioembolization, with special discussions on the practical aspects of each modality including scientific rationale, number of treatment sessions, adverse events, clinical outcomes, response assessment and ongoing clinical trials.

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DIAGNOSIS AND STAGING OF HCC

HCC is diagnostic in cirrhotic livers when there is an arterially enhancing lesion >1 cm with venous washout. Unless genomic marker analysis is planned, biopsy is generally not necessary, since diagnosis can be made using guidelines from the European and American Association for the Study of the Liver.[4, 5] This is followed by a thorough evaluation of the patient including history and physical examination, assessment of laboratory values, imaging and determination of baseline performance status. Selection of a specific therapy by the BCLC staging system is based on the tumor characteristics, Child-Pugh stage and performance status. Although treatment recommendations are available for all BCLC stages, up to 50% of patients cannot receive the recommended treatment modality. As a result, cTACE, DEB-TACE and radioembolization play an important therapeutic role across many BCLC stages. A multidisciplinary team (hepatology, medical/surgical oncology, transplant surgery, interventional radiology) should be considered the optimal model when making treatment recommendations to HCC patients.

EMBOLOTHERAPY: MECHANISM OF ACTION

Arterial embolotherapies are based on the fact that while the normal hepatic parenchyma derives its blood supply primarily from the portal vein (75%), hepatocellular carcinoma (HCC) derives all of its blood supply from the hepatic artery. Hence, while tumors grow in size, the hepatic arterial blood supply also hypertrophies. Capitalizing on this mechanism, hepatic arterial catheterization can be exploited in order to deliver a therapeutic (drug, radiation), in the hypertrophied vessels, eventually lodging near or within the target, depending on the size of the agent administered (Figure 1). In the case of cTACE, lipiodol is mixed with one or more chemotherapeutics (doxorubicin, cisplatin, mitomycin) and injected within the target vessel. Lipiodol acts as a delivery vehicle for the agents and ultimately lodges near the tumor. DEB-TACE, the evolution of cTACE, involves the loading of drug (doxorubicin) in drug-eluting microspheres; once injected near the tumor, a slow and controlled release of the drug results in anti-tumoral effects. Finally, with radioembolization, 30-micron sized particles are injected and ultimately lodge within the tumor. A low dose-rate brachytherapy is applied to the tumor during the radioactive decay process. While all 3 of these treatments appear to share similarities, there are distinct differences in patient selection, technique, patient monitoring and complications. All have achieved encouraging clinical outcomes in terms of response, time-to-progression (TTP) and overall survival. Given these outcomes, all are gaining acceptance for treating appropriately selected HCC patients.

CONVENTIONAL CHEMOEMBOLIZATION (cTACE)

cTACE is defined as the delivery of one or more chemotherapeutics directly to the tumor via hepatic arterial injection[6]. This method has been in clinical practice since the 1980s and represents the mainstay of embolotherapy worldwide.[7, 8] Although controversial, the most commonly used drugs for cTACE include doxorubicin alone or in combination with mitomycin C and/or cisplatin. The triple-drug combination is the preferred method in the United States.[9]

Patient Selection

cTACE is indicated in HCC patients with preserved performance status and liver function without vascular invasion or extrahepatic disease. In general, contraindications include intractable systemic infection, leukopenia (white blood cell count <1000/ul), cardiac/renal insufficiency (serum creatinine >2.0 mg/dl), hepatic encephalopathy, performance status >2, hepatofugal flow and biliary obstruction. [10, 11]

Procedure

Once a patient has been deemed a candidate for cTACE, a thorough pre-treatment preparation is required. Patients are typically admitted the morning of the procedure for hydration, antibiotics (optional), anti-emetic and narcotic loading. The procedure is performed using a common femoral artery catheterization (same for DEB-TACE and radioembolization), and the lipiodol/chemotherapy emulsion is administered to the hepatic artery perfusing the tumor(s).[11] The vehicle used for chemotherapy delivery is lipiodol, a poppy seed oil containing 38% Iodine by weight. In order to obtain an embolic effect and prevent washout of the drug, 100–500 um bland occlusive particles are subsequently injected[12]. Lipiodol permits the drug to concentrate in the tumor and is retained for weeks; normal hepatocytes excretion is seven days. Immediately following cTACE, a non-contrast CT is obtained demonstrating the proper location of the chemotherapy/lipiodol combination (Figures 2a, 2b). The standard approach to cTACE is for repeated treatments at 2–4 month intervals, depending on the tumor burden and response.

Clinical Outcomes with cTACE

Lo and Llovet published 2 separate studies establishing the benefit of cTACE in patients in HCC. Both studies used repeated, fixed-interval (intention-to-treat) chemoembolization compared to best supportive care.[13, 14] They concluded that cTACE improved survival in patients with unresectable HCC. In a large phase 2 study, Takayasu published data from a large cohort study of 8510 HCC patients treated with cTACE describing liver function, alpha-fetoprotein, tumor size, number of lesions, and portal vein invasion as significant prognosticators of survival.[15] These findings were later confirmed with a meta-analysis of seven published randomized control trials concluding that cTACE is an effective palliative treatment modality for unresectable HCC.[16] Lewandowski reported on a recent comprehensive imaging and long-term survival analysis in a cohort of 172 patients following cTACE. Median survival was significantly different between patients with BCLC stages A, B and C disease (Stage A: 40.0 months; B: 17.4 months; C: 6.3 months; P<.0001). The study concluded that chemoembolization was safe and effective in patients with HCC; however, TTP and survival was confounded by tumor biology and background cirrhosis.[17] Most recently, Takayasu published another large cohort of 4966 HCC patients.[18] As opposed to the Lewandowski series, the recent Japanese study excluded patients with vascular invasion, extrahepatic metastases and prior treatment. Applying these selection criteria, excellent results were achieved (median survival 3.3 years), with Child-Pugh class, tumor number, size, alpha-fetoprotein, and des-gamma carboxy-prothrombin levels being independent predictors of survival.

Adverse Events and Complications

Post-embolization syndrome, manifest by pain, nausea and vomiting, is managed during the hospitalization (1–3 days). Other complications may include: a) biliary duct injury (up to 5.3%), [1920] b) liver abscesses in patients following biliary interventions (stents, sphincterotomy), [19] c) duodenal or gastric ulcers from inadvertent deposition of the chemotherapeutic agents, [19] d) vascular injury such as spasm/dissection from repeated chemotherapy injection in the arterial system, [21] e) and tumor rupture (<1%).[19]

DRUG-ELUTING BEAD CHEMOEMBOLIZATION (DEB-TACE)

The concept of DEB-TACE builds on the rationale for cTACE. Through a drug-loading process, the microspheres are able to absorb the chemotherapeutic agent. These unique properties permit for release of drug in a controlled and sustained manner. This leads to a significant reduction of peak plasma concentration when compared to cTACE.[26] The mechanism of drug-elution is based on a strong drug-bead interaction that can be attributed

to an ionic exchange process between anionic drug moieties and the hydrogel sulfonate or carboxyl counter ions[22, 23] .

Patient Selection

In general, patients in the intermediate BCLC B category may be considered for DEB-TACE, provided they have preserved performance status and liver function. However, in accordance with clinical trials that have been completed with DEB-TACE, ideal patients should have HCC that can be isolated angiographically, such that selective (as opposed to lobar) injections can be performed. Similar to cTACE, the microspheres are infused slowly while the delivery to tumor is performed. Treatment guidelines for DEB-TACE recommend up to 4 treatments within 6 months to the entire treatment field.[24]

Clinical Outcomes with DEB-TACE

There have been several studies reporting on outcomes with DEB-TACE. [25, 26] As mentioned earlier, the rationale is one of increased intra-tumoral retention and decreased bioavailability, translating into lower toxicity rates. In an early study, Poon et al reported a 63% response using the modified RECIST criteria.[27] A recent randomized controlled trial on 212 patients comparing conventional TACE with DEBs failed to show an improvement in response using the more controlled drug-eluting methodology. However, in a subset analysis, more advanced patients were better able to tolerate DEB-TACE compared with cTACE. [28] In a recent retrospective analysis, Dhanasekran et al concluded that transcatheter therapy with DEB-TACE offered a survival benefit over conventional chemoembolization in patients with unresectable HCC.[29] There were fewer adverse events when compared to cTACE, further supporting the safety profile of DEB-TACE.

Varela et al reported on a small 27 patient series of DEB-TACE in HCC and Child-Pugh A cirrhosis. They demonstrated that response rate was 75% by CT at 6 months, with systemic doxorubicin levels significantly lower than cTACE. One and 2-year survival rates were 92.5% and 88.9% respectively, with a median follow up of 27.6 months. They concluded that chemoembolization using DEBs is an effective procedure with a favorable pharmacokinetic profile.[30] The same group recently reported on a 104-patient cohort of hyperselected (preserved synthetic function and performance status) treated with DEB-TACE. They reported a median survival of 48 months, challenging current thinking on the 20–22 month expected outcomes in intermediate BCLC B patients[31]. The combination of Sorafenib and DEB-TACE was also shown to be safe in a recent 35 patient cohort, resulting in a response rate of 58% by necrosis criteria.[32]

Recently, Malagari et al performed a prospective randomized trial comparing DEB-TACE to bland embolization. Although a partial imaging response to therapy was similar between the groups, TTP was longer in the DEB-TACE arm, establishing that the chemotherapy, along with embolization, plays an important role in the cytotoxic effects.[33] The same group also expanded their analysis into a 173 patient cohort and a 5-year survival analysis. Outcomes replicated those reported by other investigators, with median survival exceeding 43 months.[34] Clinical outcomes of cTACE and DEB-TACE are summarized in Table 1.

Complications

Recent studies, including a 237 patient cohort, have reported on the safety profile of DEB-TACE. Although the systemic exposure is reduced with controlled release of drug in the tumor microenvironment, adverse events seen with DEB-TACE are similar to (but lower in frequency than) cTACE. These include pain, nausea, vascular injury, hepatic failure, abscess formation and tumor rupture.[35, 36]

RADIOEMBOLIZATION

The technique of radioembolization involves the delivery of high dose radiation via the hepatic arterial system. This is distinctly different from external beam radiation therapy, where dose limitations and hepatic radiosensitivity limit the amount that can be delivered to hepatic tissue before the development of radiation-induced liver disease (ascites, anicteric hepatomegaly, elevation of alkaline phosphatase).[3, 37, 38] High dose 30-micron sized radioactive particles are delivered to the tumor at the segmental or lobar level. In contradistinction to cTACE/DEB-TACE, vessel occlusion is not the intent with radioembolization. Rather, the microspheres lodge without causing occlusion at the macroscopic level and emit beta radiation[39]. Consequently, since vessel occlusion does not occur, hospitalization is not required. Patients are discharged 2–6 hours on the same day following radioembolization.

Patient Selection

As more experience with radioembolization has been garnered over the last decade, certain clinical observations have been made. First, although the concept of segmental injections in HCC is the standard for most embolotherapies, radioembolization, with an improved toxicity profile, appears to play a role in more advanced disease[40–42]. This includes patients with performance status 1–2, multifocal disease with or without PVT. Since segmental injections are not mandated, lobar infusions treating larger territory of disease is routine[43]. Second, while cTACE/DEB-TACE requires inpatient hospitalization, radioembolization has shifted the embolotherapy paradigm into one of outpatient therapies, translating in better quality-of-life[41, 42]. Finally, in contradistinction to routine, scheduled embolizations with cTACE/DEB-TACE, radioembolization patients receive 1 treatment, with follow-up sessions on an as-needed basis.

Clinical Outcomes with Radioembolization

Several large phase 2 studies have been published describing long-term outcomes with radioembolization. A 291-patient comprehensive cohort was the first to describe toxicity, imaging and survival outcomes stratified by BCLC, United Network for Organ Sharing, tumor stage and Child-Pugh[44]. This study was also the first to describe TTP outcomes in granular detail, serving as background data for comparative studies. Subsequently, a 108-patient study from Germany validated these outcomes in advanced patients, confirming the reproducibility of this technique and equivalent outcomes to cTACE/DEB-TACE[45]. A 325-patient study followed, further confirming long-term survival outcomes stratified by BCLC stages[46]. Finally, most recently, a phase 2 study from the group in Italy described the role of radioembolization in intermediate/advanced patients. This last report served to launch a randomized phase 3 study comparing radioembolization to Sorafenib[47].

While there has been no randomized study comparing radioembolization to chemoembolization, a comparative effectiveness report described outcomes in a 245-patient cohort. The authors reported that adverse events, clinical toxicities, response rate and TTP were improved with radioembolization when compared with cTACE. However, overall survival was no different, likely as a result of competing risks of death of HCC and cirrhosis. The study also challenged the concept of TTP being a surrogate of survival in HCC. On post-hoc analyses, it was concluded that a sample size of >1000 patients would be required to establish survival equivalence between cTACE and radioembolization[40]. The improvement in TTP was also confirmed by another comparative report, demonstrating that radioembolization outperformed cTACE in downstaging to transplantation (Figures 3a, 3b).[48] Finally, Kulik reported on the niche clinical application of radioembolization in PVT, reporting on the safety profile in this advanced patient population. The authors confirmed

that radioembolization could be used in vascular invasion without the risk of ischemic hepatitis[43, 49]. These findings were recently further confirmed by the same group[49]. Clinical outcomes of radioembolization are summarized in Table 2.

Complications

Adverse events from radioembolization are distinctly different than other embolotherapies. The dominant side-effect is fatigue, with other adverse events including non-target deposition of microspheres (possibly leading to ulcer formation), fibrosis/scarring of the liver parenchyma and cholecystitis. Radiation-induced liver disease is rare when proper patient selection criteria are applied[38, 50].

ASSESSING RESPONSE FOLLOWING EMBOLOTHERAPY

Assessing response to locoregional therapies can be complex. In contradistinction to systemic treatments where all tumors are simultaneously exposed to the agent, this is not the case with embolotherapy. During the course of treatment with embolization, lesions are treated at different times at staged 4–6 week intervals. Hence, response is often assessed in the treated lesion, while untreated lesions are only incorporated once the entire treatment field has been completed.[51] Although size criteria are the most common reporting standards, methods using necrosis have been implemented in order to incorporate the mechanism of action of embolization. However, given the lack of standardization of these methods, overall tumor size reduction is still considered the gold standard. In 1979, the World Health Organization (bi-dimensional measurements) published guidance on the anatomical assessment of tumor response to therapy.[52]http://jama.ama-assn.org/cgi/content/full/303/11/1062-REF-JOC05021-8 This further evolved to the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines (uni-dimensional measurements).[53] The European Association for Study of the Liver guideline was based on percent change in amount of enhancing tumoral tissue (necrosis).[5, 53, 54] Recently, the modified RECIST assessment (mRECIST) were published, formally recommending the concept of viable tumor tissue (arterial phase of contrast-enhanced imaging) and aimed to provide a common framework for the imaging response of clinical trials in HCC.[55] The field of response assessment following local therapies is dynamic, with studies investigating the optimal number of target lesions, pathology correlates and scoring systems, patterns of disease progression, surrogates of survival and biomarkers[51, 56–62].

ONGOING TRIALS

Research in embolotherapy continues to be a very active. Given that cTACE and Sorafenib have both shown to provide a survival advantage, studies with radioembolization have been proposed to either compete against or combine with these other standards of care. Recently, the equivocal findings from a trial using DEB-TACE +/− Sorafenib were announced.[63] This study was unable to definitively confirm a role for Sorafenib in combination with embolization. Cooperative groups are also carrying out similar studies in order to further investigate the role of Sorafenib in HCC patients undergoing embolization. There are also several ongoing trials comparing cTACE and radioembolization in randomized designs with TTP as the endpoint (incorporating quality-of-life, econometrics). Finally, there are other studies looking at the role of radioembolization in combination with or comparison to Sorafenib in the advanced patient population. These trials are robust in their rationale, statistical design (international, multicenter, randomized phase III) and primary endpoints (survival)[64]. Final results of these seminal studies are expected within the next 3–5 years.

CONCLUSION

Chemoembolization and radioembolization are trans-arterial locoregional therapies that have gained widespread recognition for the treatment of HCC. Although a randomized trial comparing cTACE and DEB-TACE did not reach its endpoint, there appears to be better tolerability in more advanced patients with DEB-TACE. Similarly, while a comparative effectiveness study of cTACE and radioembolization did not show a survival advantage, Y90 patients did exhibit lower toxicities and longer TTP. Currently enrolling studies combining these arterial locoregional therapies with targeted systemic therapies are underway. As the results of randomized studies of embolotherapy combined with systemic agents mature, the clinical indications and specific patients ideally suited for these palliative interventions will continue to be refined.

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Abbreviations

BCLC	Barcelona Clinic Liver Cancer
cTACE	Conventional trans-arterial chemoembolization
DEB-TACE	Drug-eluting bead trans-arterial chemoembolization
EASL	European Association for the Study of the Liver
HCC	Hepatocellular Carcinoma
PVT	Portal venous thrombosis
TACE	Trans-arterial chemoembolization
TTP	time-to-progression
^{90}Y	Yttrium-90 radioembolization

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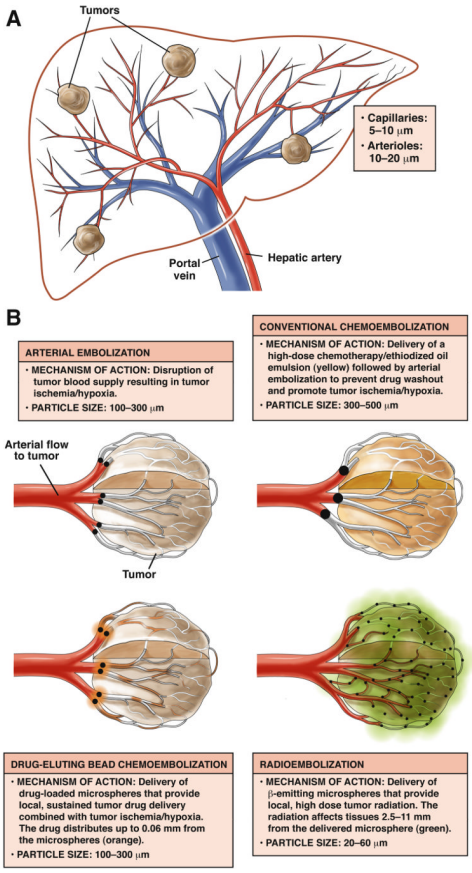
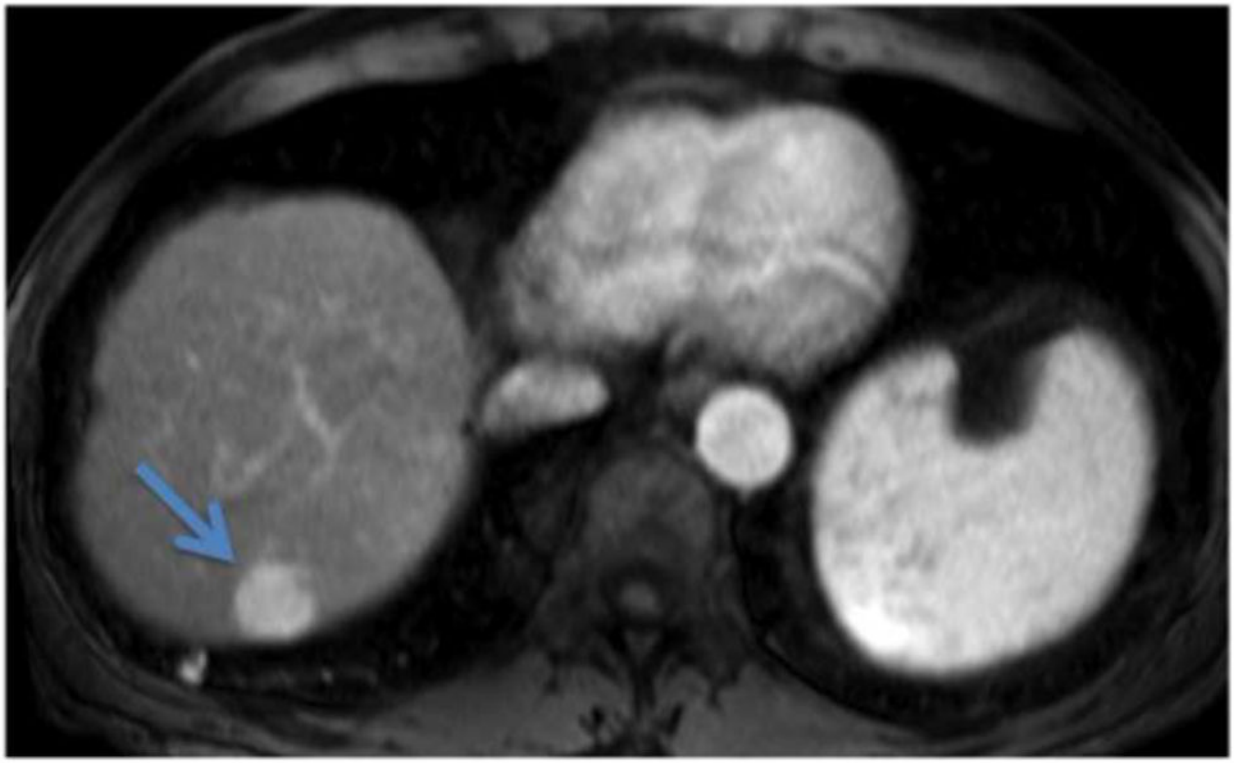


Figure 1.

Figure 1a. Schema depicting arterial blood supply to hepatocellular carcinoma.

Figure 1b. Demonstration of mechanism of action of bland, chemoembolization, drug-eluting beads and radioembolization.

Figure 2a



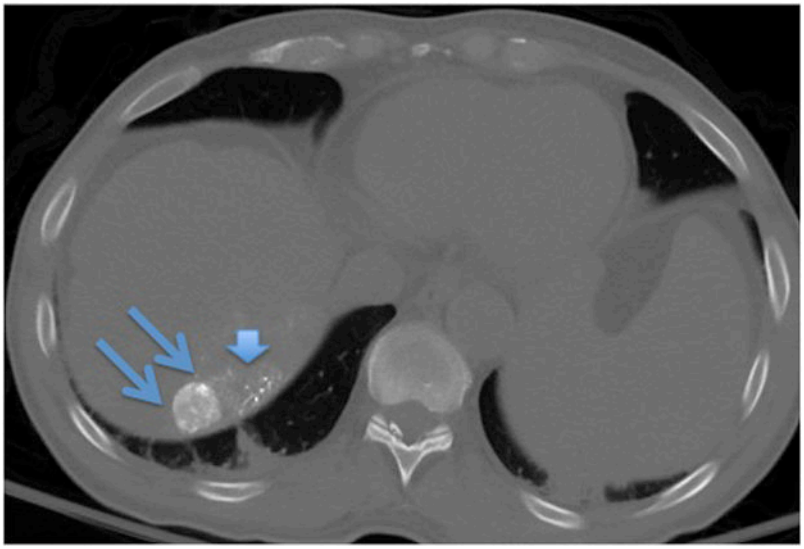


Figure 2.

Figure 2a. T1-Weighted gadolinium-enhanced MRI reveals a focal enhancing mass in hepatic segment 7 (arrow). This mass demonstrated venous phase contrast washout, meeting the guidelines for HCC. After discussion at multidiscipline tumor board, this non-operative candidate underwent cTACE.

Figure 2b. A non-contrast CT scan performed immediately after cTACE revealed focal uptake of Lipiodol within the targeted tumor (double arrows). There is some non-target Lipiodol uptake in the non-cancerous hepatic parenchyma (arrow head) adjacent to the tumor.

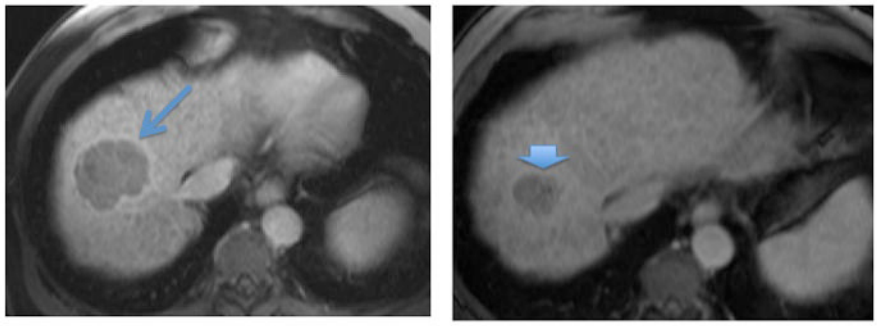


Figure 3.

Figure 3a. Gadolinium-enhanced MRI (venous phase) showing a 6 cm mass in the hepatic dome (arrow). This tumor showed early phase arterial enhancement, consistent with HCC. This tumor is outside of the Milan transplant criteria.

Figure 3b. Gadolinium-enhanced MRI 6 months following Y90 radioembolization. The tumor is now 3 × 3 cm (arrowhead) and is within Milan transplant criteria. This patient underwent liver transplantation.

Table 1

Outcomes of cTACE and DEB-TACE in Hepatocellular Carcinoma

	Takayasu et al[15]	Lewandowski et al[17]	Takayasu et al[17]	Lammer et al[28]	Malagari et al[33]	Malagari et al[31]	Pawlik et al[32]	Burrel et al[31]
Purpose	Analyze survival after TACE	Determine imaging and survival outcome after TACE	Discern the best indication and appropriateness of the current treatment algorithm for TACE	Compare response rate and toxicities of cTACE with DEB-TACE	Compare DEB-TACE with bland embolization	Report on the 5-year survival of HCC patients treated with DEB-TACE on schedule	Report on outcomes of patients treated with DEB-TACE and Sorafenib	Discern survival of selected patients (preserved liver function, absence of symptoms, extrahepatic spread or vascular invasion) treated with DEB-TACE
Patients	8510	172	4966	cTACE:108 DEB-TACE: 93	DEB-TACE: 41 Bland: 43	173	35	104
Response rate	-	WHO: 31% EASL: 64%	-	cTACE: 22% DEB-TACE:27%	DEB-TACE:73.1% Bland: 60%	EASL CR:23% EASL PR: 48%	EASL: 58%	-
TTP (months)	-	7.9	-	-	DEB-TACE: 10.6 Bland embolization:9.1	-	-	-
Survival	1-year: 82% 3-year: 47% 5-year: 47%	BCLC A: 40.0 mo BCLC B: 17.4 mo BCLC C: 6.3 mo	1-year: 87% 3-year: 55% 5-year: 34%	-	No difference between two groups within 1 year	1-year: 93.6% 3-year: 62% 5-year: 22.5%	-	Overall: 48.6 mo BCLC A: 54.2 mo BCLC B: 47.7 mo

Abbreviations: BCLC: Barcelona Clinic Liver Cancer; cTACE: conventional transarterial chemoembolization; DEB-TACE: drug-eluting bead transarterial chemoembolization; EASL: European Association for the Study of the Liver; TACE: transarterial chemoembolization; WHO: World Health Organization

Table 2

Outcomes of radioembolization in Hepatocellular Carcinoma

	Salem et al[44]	Hilgard et al[45]	Sangro et al[46]	Salem et al[40]	Mazzaferro et al[41]
Purpose	Assess clinical outcomes of patients treated with Y90	Assess clinical outcomes of patients treated with Y90 in Europe	Evaluate prognostic factors of survival after Y90 in European patients	Compare the effectiveness of Y90 vs. cTACE	Provide a prospective assessment of safety and efficacy for Y90 treatment of patients with intermediate and advanced disease
Patients	291	108	325	Y90: 123 TACE: 122	52
Response rate	WHO: 42% EASL:57%	EASL: 40%	-	Y90: 49% TACE: 36%	WHO: 40% EASL: 40%
TTP (months)	7.9	10	-	Y90: 13.3 TACE: 8.4	11
Survival (months)	Child-Pugh A:17.2 Child-Pugh B:7.7	16.4	BCLC A: 24.4 BCLC B: 16.9 BCLC C: 10.0	Y90:20.5 TACE: 17.4	15

Abbreviations: BCLC: Barcelona Clinic Liver Cancer; EASL: European Association for the Study of the Liver; RECIST: Response Evaluation Criteria in Solid Tumors; TACE: transarterial chemoembolization; TTP: Time-to-progression; WHO: World Health Organization