Interventional Radiology Management of Unresectable Intrahepatic Cholangiocarcinoma

Adam D. Talenfeld, Daniel J. Holzwanger, and David C. Madoff

Contents

Abstract

Inoperable intrahepatic cholangiocarcinoma (ICC) carries a dismal prognosis. Transarterial therapies have been shown by numerous small- and medium-sized series to prolong survival in these patients well beyond 1 year. Studies of drug-eluting bead transarterial chemoembolization (DEB-TACE) and yttrium-90 transarterial radioembolization (TARE) suggest longer survival may be achieved with these newer transarterial modalities. Research to date suggests that patient factors associated with prolonged survival after transarterial therapy include the absence of cirrhosis or the presence of at most Child A cirrhosis, normal or near normal performance status (Eastern Cooperative Oncology Group, ECOG, 0–1), peripheral tumor morphology, tumor hypervascularity, small tumor size, low tumor grade, low tumor burden, and the absence of portal thrombus. The presence of extrahepatic disease has not been found significantly to impact survival, confirming the high mortality from the primary disease. Several studies have directly compared different transarterial therapies. Several have found that transarterial chemoembolic (TACE) therapy is more effective than transarterial chemoinfusion (TACI); however, no study has been conducted to evaluate whether this difference between TACE and TACI persists in the subpopulation of hypovascular tumors. There is evidence that dual-agent conventional TACE with gemcitabine and cisplatin may be more effective than single-agent TACE. In addition to progress being made with transarterial therapies, early results of percutaneous thermal ablation for selected patients with small-to-moderate-sized unresectable ICC are promising. Three recent studies of patients receiving thermal ablation each reported median overall survival of over 30 months post-treatment. Prospective studies of transarterial and percutaneous ablative therapies are needed.

A. D. Talenfeld · D. J. Holzwanger · D. C. Madoff (✉)
Department of Radiology, Division of Interventional Radiology, New York-Presbyterian Hospital, Weill Cornell Medical Center, 525 E. 68th St.,P-518, New York, NY 10065, USA
e-mail: dcm9006@med.cornell.edu

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1 Introduction

The prognosis for patients diagnosed with intrahepatic cholangiocarcinoma (ICC) remains poor. Surgical resection is the only established curative option for patients with ICC, and only 30 % of those diagnosed with this disease are eligible for resection at the time of diagnosis [1]. With surgery, 5-year survival has been reported at rates ranging from 14 to 40 % [2]. While there has been incremental progress through the years, traditional nonsurgical options of systemic chemotherapy and external beam radiation have yet to significantly alter the course of disease. Over the last decade, transarterial and percutaneous ablative therapies have become the standard of care for unresectable hepatocellular carcinoma (HCC). This has in recent years led to the incorporation of these interventional treatment modalities in the case of those suffering from unresectable ICC. This chapter describes the indications for and general techniques of transarterial therapies for ICC, followed by a summary of the current scientific literature supporting effectiveness and associated complications. Finally, recent studies of ICC successfully treated with percutaneous thermal ablation will be reviewed.

2 Indications for and General Technique of Transarterial Therapy

2.1 Indications and Contraindications

Transarterial embolization (TAE), chemoembolization (TACE), chemoinfusion (TACI), and most recently radioembolization (TARE) are indicated for patients with unresectable ICC that is either isolated to the liver or predominantly localized within the liver and likely to be the patient's principal source of morbidity and mortality.

Contraindications to transarterial therapies can be organized according to the different elements of the procedure being considered: angiography, chemotherapy, embolization, and/or radiation therapy. Absolute contraindications to angiography are few and include, principally, severe anaphylactoid reaction to radiographic contrast media and uncorrectable coagulopathy. Contraindications to the administration of chemotherapy generally include thrombocytopenia (<50,000 platelets) or leukopenia (white blood cell count <1000), renal insufficiency (creatinine >2 mg/dL), and severe cardiac or pulmonary disease (e.g., NYHA III or IV congestive heart failure). These chemotherapy contraindications may be considered relative since transarterial therapies largely bypass the systemic circulation.

Most of what is known regarding contraindications for transarterial embolic therapies in ICC is derived from that which has been established in the treatment for HCC. There are few absolute contraindications to transarterial embolic therapies as a whole, but there are several relative contraindications. Decompensate liver disease (Child-Pugh class C cirrhosis) is generally considered a contraindication to transarterial embolization, since any further deterioration liver function or worsening of portal hypertension brought on by even partial or temporary occlusion of arterial supply can provoke liver failure or a life-threatening complication such as esophageal variceal hemorrhage. The Child-Pugh scoring system has been shown to be a better predictor of survival in HCC patients treated with TACE than the Model for End-stage Liver Disease (MELD) score; however, a MELD score greater than 10 has also been negatively associated with survival after transarterial therapy for HCC [3]. Poor performance status is, likewise, a relative contraindication to embolization. While no exact cutoff has been described, generally an Eastern Cooperative Oncology Group (ECOG) score >2 or Karnofsky index <70 % signals a patient without sufficient hepatic functional or systemic reserve to allow for safe treatment.

There is no individual laboratory value that represents an absolute contraindication to transarterial embolic therapy. Serum total bilirubin >3.0 mg/dL has been described as a contraindication to lobar treatment; however, the degree of hepatic arterial occlusion is largely subject to control by the treating interventional radiologist based on the type, quantity and location of embolic infusion. Many would argue this limit need not apply to segmental or subsegmental embolic treatment, as very little hepatic arterial supply maybe sacrificed in this setting. The constellation of >50 % liver volume replacement by tumor, serum bilirubin >2.0 mg/dL, lactate dehydrogenase >425 mg/dL, and aspartate aminotransferase (AST) >100 IU/L has a strong anecdotal association with post-treatment mortality; however, individual elevations of these laboratory values are of uncertain significance.

The absence of an intact sphincter of Oddi is a relative contraindication that raises significantly the risk of abscess complicating any transarterial embolic intervention. Society of Interventional Radiology (SIR) and Cardiovascular and Interventional Radiology Society of Europe (CIRSE) guidelines recommend that tumor burden generally be less than 50 % of liver volume. Society guidelines also advise that there be antegrade flow in the main portal vein or well-established collaterals; however, some exceptions exist in the form of less embolic therapies, such as may be achieved with certain drug-eluting bead formulations [4, 5].

Portal vein thrombus is also less of a concern with TARE, since the radiomicrospheres, which range from 20 to 60 microns in diameter and are rarely infused in greater than 1 mL volumes, serve as carriers of yttrium-90 radioisotope rather than primarily as agents of arterial occlusion. From

data gathered in treatment for liver tumors with external beam therapy, a 50 Gy whole-liver limit has been established beyond which radiation-induced liver disease (RILD) has been known to occur. For this reason and because some radiomicrospheres will inevitably pass through the hepatic sinusoids and tumor microcirculation into the hepatic veins and the lungs, TARE is always preceded by mapping angiography and test administration of 99 mTc-labeled macroaggregated albumin (MAA) radiotracer and calculation of the fraction of radiopharmaceutical shunted to the lungs. A maximum of 30 Gy administered to the lungs in a single treatment or 50 Gy cumulatively has been established in order to prevent radiation-induced pulmonary fibrosis. In practice, doses to the lungs are routinely well below these thresholds. When large or diffuse liver tumors warrant administration of more radioactivity, doses can usually be reduced as necessary to balance safety to the lungs with need for therapeutic activity in the liver.

Extreme care must be taken during mapping angiography to identify any artery arising from the hepatic circulation providing supply the other organs of the foregut. When these are found, they should be treated with coil embolization. Failure to do so has been associated with severe toxicity in the form of pain and gastrointestinal ulceration which may be refractory to treatment. In the rare case of hepaticoenteric collateral arterial anatomy that cannot be corrected or avoided, TARE is absolutely contraindicated.

2.2 Transarterial Technique and Periprocedural Care

2.2.1 Preprocedure Preparation

The plan for transarterial treatment should optimally be established during discussion at an institutional tumor board or other interdisciplinary meeting during which imaging is reviewed and unresectability of the tumor is established. The nature, purpose, risks and alternatives of the planned treatment are explained to the patient by the interventional radiologist during a separate office visit prior to the day of treatment. In addition to setting appropriate patient expectations for treatment, any additional bloodwork, imaging, medical clearance, or anesthesiology assistance can be arranged as necessary at this time. Relevant laboratories include a complete blood count, prothrombin time, basic metabolic panel, liver function tests, and CA 19–9 tumor marker. Dedicated triphasic CT or MRI should generally be acquired within 30 days of the planned intervention to inform the interventionalist of proximal visceral arterial anatomy and ensure appropriate preprocedure staging.

For patients undergoing TARE, mapping angiography with coil occlusion of hepaticoenteric collateral arteries prior to the day of treatment is essential. This is generally performed as an outpatient procedure during which detailed interrogation of arterial supply to the tumor is identified with conventional and rotational angiography. Multiplanar CT reconstructions from rotational angiograms (also known as C-arm or cone-beam CT) are routinely obtained from rotational angiograms. Review of these images can be tremendously helpful in identifying vessels supplying target tumors or extrahepatic tissues that would be jeopardized by nontarget radioembolization. Parenchymal- and venous-phase images obtained from prolonging conventional arterial angiograms are also helpful in identifying these vessels. Techniques for identifying additional normal and variant hepaticoenteric collateral arteries are beyond the scope of this publication, but meticulous technique is required. In patients with native foregut anatomy, coil embolization is routinely performed in the gastroduodenal and right gastric arteries without adverse sequelae. Recently, a microcatheter with a deployable cone tip designed to prevent reflux of microspheres proximal to the site of infusion has been developed (Surefire infusion system; Surefire Medical, Inc., Westminster, CO) and described in the literature with the goal of reducing or avoiding altogether the need for coil embolization during mapping angiography [6]. After skeletonization of the hepatic arterial supply, 99 mTc-MAA radiotracer is injected in the expected site of future TARE, and the patient is routinely evaluated by planar and SPECT-CT for lung shunt calculation and the presence of any extrahepatic deposition of radiopharmaceutical.

Antiplatelet agents, anticoagulation, and insulin are generally held prior to the day of any transarterial procedure. For transarterial therapies, 81 mg aspirin is generally not withheld, and 325 mg aspirin is held or continued at the interventional radiologist's discretion, taking into consideration the patient's cardiovascular risk. Patients are instructed to be NPO except their other routine medications with sips of water for 8 hours prior to the time of the planned procedure. Peripheral venous access is obtained, and intravenous hydration with 150–300 mL/h normal saline is routinely administered unless cardiac or renal function requires fluid restriction, in which case lower rates may be used. Although high-level evidence is lacking, antibiotic prophylaxis to cover skin and enteric flora are generally administered within an hour of procedure commencement. For patients without an intact sphincter of Oddi, bowel preparation beginning the night before the procedure and additional antibiotic prophylaxis for 1–2 weeks may also be beneficial at reducing abscess formation. Anti-emetics, steroids, and proton pump inhibitors may also frequently be administered.

2.2.2 Procedure

Transarterial therapies are performed under moderate sedation with independent radiology nursing supervision for

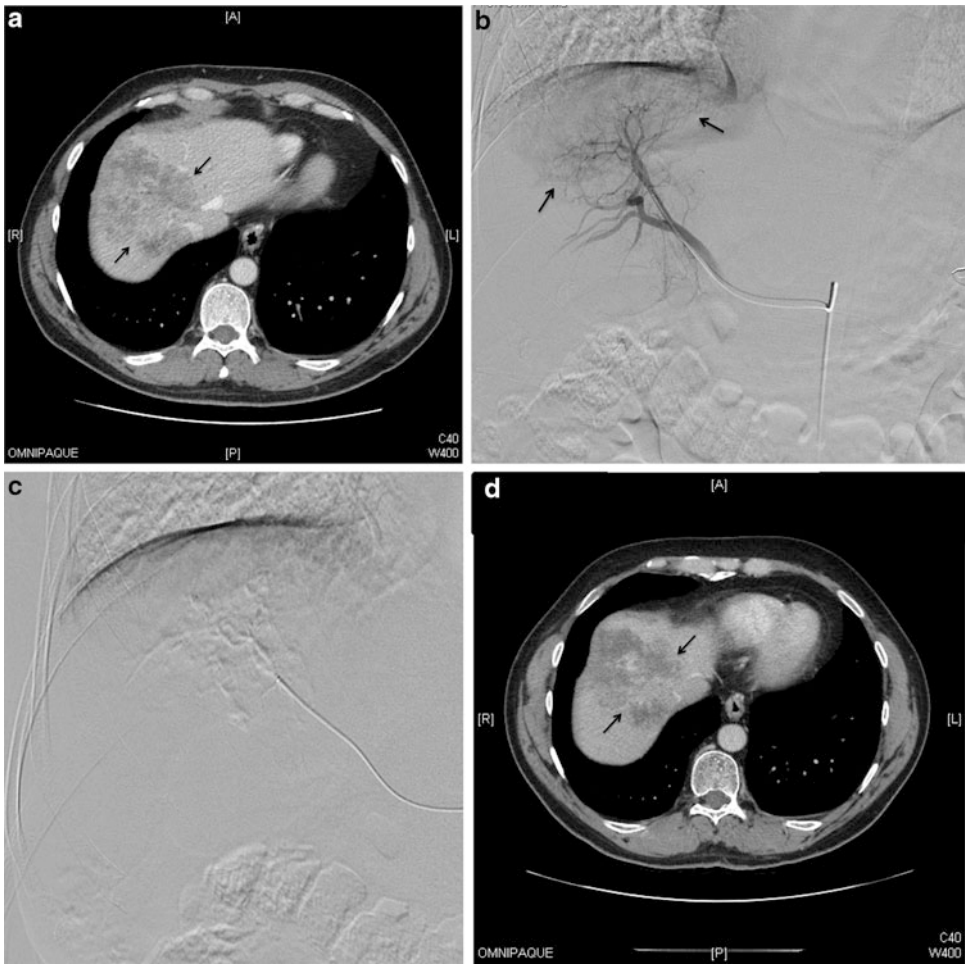


Fig. 1 49-year-old man with unresectable, liver-dominant intrahepatic ICC. **a** Axial portal-phase post-contrast CT image demonstrating a heterogeneously hypoenhancing mass centered in segments 7 and 8, measuring up to 9.8 cm. **b** Segmental right hepatic artery angiography demonstrating tumor blush and discrete neovascularity despite relative hypovascularity by CT. **c** Follow-up angiography immediately after embolization to segmental vessel stasis with 100 micron Embozene microsphere permanent embolic (CeloNova, Ulm, Germany) demonstrates subtraction artifact from casts of the embolized tumor vessels due to static contrast trapped between microspheres. **d** Follow-up axial portal-phase post-contrast CT image 2 months after embolization demonstrating decreased enhancement and slight decrease in size from 9.8 to 8.4 cm maximally

most patients, including pulse oximetry, cardiac, and blood pressure monitoring. When warranted by a patient's comorbidities, procedures may be performed with light sedation or under deep sedation with anesthesiology assistance. Recently, the wide availability of advanced cross-sectional imaging has allowed the interventionalist to forego aortic and superior mesenteric artery angiography unless arterial pathology or variant anatomy require, thus reducing X-ray exposure and contrast dose at the time of intervention. Focused sonographic examination in the IR suite may also often allow confirmation of portal patency and hepatopetal flow.

Although transradial access for TACE has been described [7], the majority of IR physicians continue to use femoral artery access. After sterile preparation, the common femoral artery is accessed using bony landmarks with or without direct sonographic guidance and a vascular sheath is placed. A reverse-curve 4 or 5 French base catheter is then advanced into the celiac artery, and lobar or segmental hepatic arterial access is obtained with a 3 French or smaller coaxial microcatheter system.

Liver function and hepatic vascular anatomy as well as tumor size, vascularity, and distribution affect the interventional radiologist's decision about where and with what to embolize. Generally, embolic treatments to more than one lobe are staged to decrease risk of liver failure and portal hypertensive complications [8]. More highly embolic treatments tend to be administered on a segmental or subsegmental level, whereas less embolic treatments may be preferred for lobar administrations in cases of more widely distributed tumor burden. Transarterial lidocaine may be administered immediately prior to embolization and has been shown to decrease pain [9].

A variety of embolic and chemotherapeutic agents are currently in use in transarterial therapy of primary hepatic malignancy. There is no adequately powered prospective trial that demonstrates improved survival for ICC or HCC by adding transarterial chemotherapy to embolization (TACE) versus transarterial embolization (TAE) alone [5]. One of two randomized, controlled trials to demonstrate superiority of TACE over best supportive care (BSC) contained a subgroup treated with transarterial embolization

without chemotherapy (also referred to as bland embolization) (Fig. 1) that had survival similar to those treated with TACE. The trial was stopped when superiority of TACE to BSC was shown, and prior to demonstration of statistical significance in the smaller bland embolization subgroup [10]. As a result of this study and another RCT that validated these findings [11], TACE has become the standard of care for unresectable HCC; however, a meta-analysis of TACE for HCC failed to show superiority of TACE over TAE [12].

There is some evidence that TACE is superior to transarterial chemoinfusion without embolization (TACI) for HCC [13]. More recently, similar data have emerged for the superior efficacy of TACE over TACI in the treatment for ICC as well [14–16]. Results of specific transarterial chemotherapeutic and embolic agents used by different practitioners will be discussed separately in conjunction with individual trials and their results; however, the endpoint of TAE and TACE is generally stasis within the distal small arteries supplying the target tumor(s).

Methodologically, TACE can broadly be divided in two categories: conventional TACE (cTACE) and TACE using drug-eluting bead (DEB-TACE). cTACE uses sterile iodinated poppy seed oil (Lipiodol Ultra-Fluid [previously Ethiodol] Guerbet, Villepinte, France) to create a viscous, radiopaque emulsion with a chemotherapeutic agent or agents that is infused into the tumoral arterial supply. This is usually followed by infusion of temporary or permanent embolic agent, though some practitioners mix the embolic agent with the chemotherapy and Lipiodol and infuse the entire suspension at once. Drug-eDEB-TACE is a modification of TACE in which a single chemotherapeutic agent is bound to the surface of a permanent embolic bead. The beads are mixed suspended in saline and contrast and usually infused without the need for any additional embolic. Once deposited in the tumoral arteries, the chemotherapeutic agent elutes off the beads over a period of several days. Two products are available. LC Beads ([marketed as DC Beads outside the USA], Biocompatibles, BTG, West Conshohocken, USA) are polyvinyl alcohol (PVA) hydrogel microspheres. QuadraSpheres ([HepaSpheres outside the USA], Merit Medical, South Jordan, USA) are hydrophilic microspheres consisting of sodium acrylate alcohol polymer that functions in similar fashion to LC Beads.

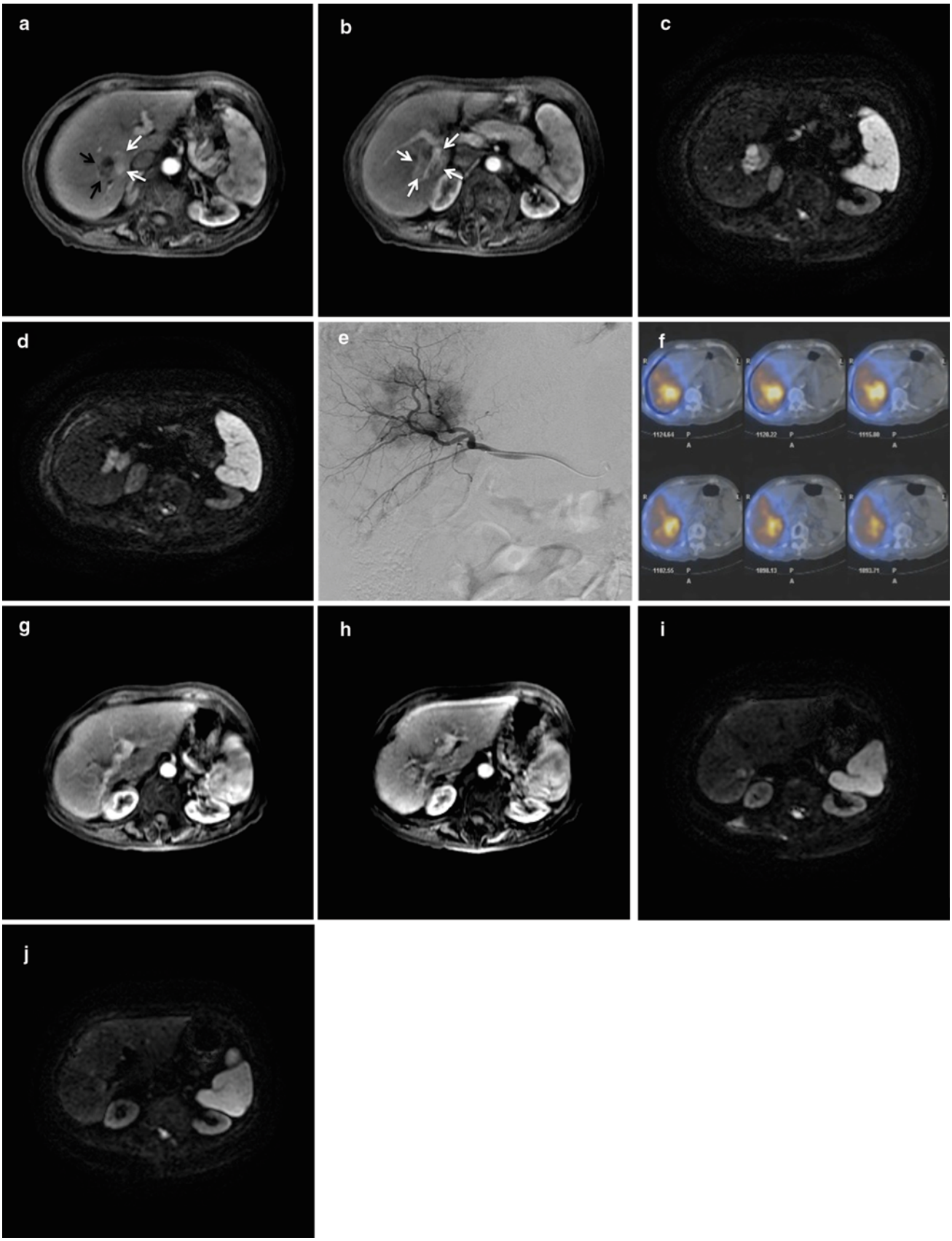
TARE, also known as selective internal radiotherapy (SIRT) or radiomicrobrachytherapy (RMB), makes use of neoplastic arterial supply to deposit small glass or starch–resin microspheres within the target tumor(s) that emit beta radiation from directly within the malignancy. Two devices are marked in North America with which to perform TARE. TheraSphere (^{90}Y microspheres; MDS Nordion, Ottawa, ON, Canada) is composed of nonbiodegradable glass microspheres with ^{90}Y as an integral constituent. TheraSphere range from 20 to 30 microns diameter and have a specific gravity of 3.6 g/dL and a specific activity of 2500 Bq/sphere. A 3-GBq vial contains 1.2×10^6 microspheres (TheraSphere package insert, MDS Nordion, Kanata, Canada). They were FDA approved in 1999 with a humanitarian device exemption (HDE) for treatment for unresectable HCC. Approval and oversight by an institutional review board is required to administer TheraSphere. Specific doses may be infused by ordering a predetermined dose-vial and coordinating the day and time of administration with published decay curves. More recently, custom dose vials have allowed greater flexibility in timing of treatment.

SIR-Spheres (Sirtex Medical, Lane Cove, Australia) are resin microspheres onto which ^{90}Y is bound. They range from 20 to 60 microns diameter and have a specific gravity of 1.6 g/dL and a specific activity of 50 Bq/sphere. A 3-GBq vial contains 40–80 $\times 10^6$ microspheres (SIR-Spheres package insert). SIR-Spheres received premarket FDA approval for treatment for hepatic metastases from colorectal cancer. Their use does not require IRB oversight, but use in any other capacity is off-label. SIR-Spheres arrive in a standard dose vial on the day of treatment. The receiving institution's radiopharmacist decants an appropriate volume of spheres to achieve the prescribed dose for treatment.

Characteristics of ^{90}Y that facilitates its use in TARE are common to both devices. ^{90}Y is a pure beta emitter that decays to stable ^{90}Zr with a half-life of 64.1 days. The average energy of beta emission is 0.9367 MeV, with a mean and maximum soft tissue penetration of 2.5 and 10 mm, respectively. One GBq (27 mCi) of ^{90}Y per kg of tissue provides a dose of 50 Gy. Doses over 80 Gy are generally considered tumoricidal. TARE takes advantage of the fact that even tumors which appear hypovascular to liver by contrast CT or MRI typically recruit additional arterial supply. There is, therefore, shunting of hepatic arterial flow toward tumors and preferential deposition of radiomicrospheres within the tumors and away from benign liver tissue. Figure 2 depicts treatment of and follow-up imaging for a patient with a partially cystic mixed hepatocellular–intrahepatic cholangiocarcinoma.

2.2.3 Post-procedure Care

After transarterial therapy, intravenous hydration, pain control, and anti-emetics are continued as needed. Some authors recommend continuing antibiotic coverage for gram-negative enteric organism in a 3–7 day course, although data for this practice are lacking [17]. A notable exception is patients lacking an intact Sphincter of Oddi. For these patients, continuation of antibiotic prophylaxis for 7-14 days post-embolization has been advocated [18]. Depending on the degree and distribution of embolization, symptoms typical of post-embolization syndrome (i.e., pain, nausea, and fatigue)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◀ **Fig. 2** 79-year-old woman with chronic hepatitis B infection and unresectable, biopsy-proven mixed hepatocellular-cholangiocarcinoma (HCC-ICC) with progression of disease on systemic chemotherapy. **a** Axial arterial-phase post-contrast MR image demonstrates a mixed cystic (*black arrows*) and solid (*white arrows*) lesion on the margin of segments 6 and 7 corresponding to biopsy-proven lesion. **b** More inferiorly, lesion is more completely solid (*white arrows*) and surrounds the posterior right portal vein. **c** pre-TARE diffusion weighted image (DWI) demonstrates markedly restricted diffusion in cystic component of mixed HCC-ICC and moderate to markedly restricted diffusion in the more medial, solid portion of the lesion. **d** pre-TARE DWI just inferior to prior image shows restricted diffusion corresponding to the HCC-ICC lesion on either side of the posterior right portal vein branch. **e** Microcatheter angiography performed via the right hepatic artery demonstrates heterogeneous tumor blush corresponding to the known partly cystic segment 6/7 tumor. **f** Axial fused SPECT-CT images from Bremsstrahlung scan immediately after transarterial radioembolization with a delivered activity of 18.6 mCi (0.69 GBq) of ^{90}Y-resin microspheres infused via the right hepatic artery: white and yellow represent areas of greatest deposition of microspheres, essentially all within the target HCC-ICC, gray is least deposition of microspheres, and light blue is blooming artifact from activity within the right liver. **g** and **h** arterial-phase axial images through the superior and inferior aspects of lesion 1 year after TARE demonstrate near complete resolution of enhancement (EASL/mRECIST complete response). **i** and **j** superior and inferior DWI 1 year after TARE demonstrates a small focus of restricted diffusion corresponding to residual cystic component of lesion. No restricted diffusion is demonstrated corresponding to any residual solid tumor. Findings in figures **g–j** are compatible with RECIST partial response and mRECIST/EASL complete response. The patient was alive and asymptomatic at the time of this publication, 12 months after TARE treatment

may require hospitalization for one or more days. In cases of highly selective embolization, patients may often be discharged on the day of treatment after ambulation criteria related to arterial puncture have been met.

2.3 Follow-up

Patients are typically followed with bloodwork and office visits 2 weeks after each treatment, although some practitioners defer office follow-up for 1 month. As described in SIR and CIRSE guidelines, triphasic pre- and post-contrast CT or pre- and dynamic post-contrast MRI should be obtained between 4 and 6 weeks after transarterial therapy and then at 3-month intervals thereafter [4, 5]. Transarterial therapies are typically repeated as warranted by imaging assessment and as long as tolerated by the patient's clinical and laboratory evidence of functional status.

3 Results

3.1 Conventional TACE and Transarterial Chemoinfusion

Table 1 summarizes results of the TACI and cTACE investigations described here, including also demographic data. Originally described in 1980 for the treatment for HCC, TACE takes advantage of the dual blood supply to benign hepatocytes (from both hepatic artery and portal vein) and the preferential recruitment of arterial neovascularity by HCC tumors to provide more effective treatment for liver tumors with fewer side effects than would be expected from systemic chemotherapy. Shown by two separate randomized, controlled trials in 2002 to improve survival over best supportive care in patients with unresectable HCC, TACE is now considered standard of care for that patient population [10, 11].

Transarterial therapy for ICC was initially reported in 2002 by Tanaka et al. using an implanted subcutaneous port attached to a microcatheter infusing in the common or proper hepatic artery, as had previously been done for HCC. With TACI, no embolic material was administered. Fluorouracil was infused periodically via the port-catheter system with or without doxorubicin, epirubicin, or mitomycin C. Tumor response by follow-up imaging was made using modified WHO criteria: complete response (CR) was disappearance of tumors, partial response (PR) was 50 % or greater reduction in maximum tumor diameter, minor response (MR) was 25–50 % diameter reduction, stable disease (SD) was less than a 25 % change in tumor size, and progressive disease (PD) was 25 % or greater increase in tumor size. Five of 11 patients (45 %) experienced PR, 2/11(18 %) had MR, 2/11 (18 %) had SD, and 2/11 (18 %) had PD. There has been criticism that the authors did not censor one patient downstaged to resection and reported mean survival after treatment initiation of 26.0 months instead of median survival, which would arguably be lower due to the downstaged patient. Nevertheless, the paper by Tanaka et al. proved the principle of transarterial therapy for ICC [19].

The first case series of TACE therapy for unresectable ICC was described by Burger et al. in 2005 in a retrospective report of 17 patients treated with one or more sessions of triple-agent chemotherapy (100 mg cisplatin, 50 mg doxorubicin hydrochloride, and 10 mg mitomycin C) emulsified with Ethiodol and followed by 300–500 micron-diameter tris-acryl gelatin microsphere embolization (Embospheres, Biosphere Medical, Rockland, MA). In keeping with modern TACE technique, the microcatheter used to administer treatment was removed at the end of each treatment session. Three patients could not be followed with MRI. Eight of 14 (57 %) patients who did receive contrast-enhanced MR exams showed >75 % tumor necrosis, and 3/14 (21 %) patients showed 25–50 % necrosis. The authors did not comment on baseline degree of tumor vascularity, and

Table 1 Results of the TACI and cTACE investigations

Primary author	Year	Study type	Type of treatment	Number of patients	Mean or median # of Rx sessions	Noncirrhotic or CP A	ECOG PS 0	ECOG PS 1	ECOG PS 2+	Prior chemotherapy (%)	Prior external beam radiotherapy (%)	Prior thermal ablation (%)
Tanaka	2002	CS	TACI: fluorouracil ± doxirubicin, epirubicin or mitomycin C	11								
Burger	2005	CS	cTACE: cisplatin, doxorubicin and mitomycin C	17	1.8	88	12	71	88	35	12	
Vogl	2006	CS	TACI: gemcitabine	12	6		25	75	0	100	8	
			cTACE: gemcitabine + starch microspheres	12	9.2		17	83	0	100	8	
Herber	2007	CS	cTACE: mitomycin C + Lipiodol	15	3.9	93			93	27		7, 7[$]
Gusani	2008	CS	cTACE: gemcitabine, cisplatin, oxaliplatin or gem-cis combo; all w/TAG microspheres	42	3.5							
Kim	2008	CS	cisplatin TACI (n = 13) or cisplatin, Lipiodol and gelfoam cTACE (n = 36)	49	3	82				4[$$]	33[$$]	
Park	2011	CC	cTACE: cisplatin, Lipiodol and gelfoam	72	2.5		65	32	3	0	0	0
			best supportive care	83			54	41	5	0	0	0
Kiefer	2011	CS	cTACE: cisplatin, doxorubicin and mitomycin C with PVA spheres	62	2.7		89	10	1	29	3	5
Shen	2011	CC	fluorouracil or carboplatin, epirubicin and hydroxycamptothecin TACI ± Lipiodol cTACE	53		60						
			no transarterial therapy	72		61						
Vogl	2012	CS	cTACE: mito C, gem, mito-gem, or mito-gem-cis, + Lipiodol and starch spheres	115	7.1	46						

(continued)

Table 1 (continued)

Primary author	Prior surgical resection (%)	Mean or median tumor size (cm)	Single tumor (%)	Peripheral morphology (%)	Unilobar disease (%)	Extrahepatic (%)	Portal vein thrombus (%)	Hypervascular tumor (%)	Treatment response imaging criteria	RECIST or WHO imaging assessment of response to treatment at 3 months or earliest post-treatment interval (% CR/PR/(MR)/SD/PD)	Median OS (months)
Tanaka	9[$]	6.7	55			36			mWHO	0/45/18(18MR)/18	26* **
Burger	12[$]	7.4	53		36	24			% tumor necrosis	57 % > 75 % necrosis, 21 % > 25 % necrosis	23***
Vogl	67				49	67			WHO	0/0/75/25	13.5* *** [#]
	50								WHO	0/0/92/8	20.2* *** [#]
Herber	7	10.8	53		40		27	87	RECIST	0/7/60/27	16.3
Gusani		9.8		12		45			RECIST	0/0/57/43	9.1
Kim		8.9	29	90		51		73	RECIST	0/20/35(tumor necrosis)/31/14	10
Park	0	8.1	43		49	54		18[##]	RECIST	0/23/67/11	12.2
	0	7.8	53		51	60		12[##]			3.3
Kiefer	11								RECIST	0/11/64/24	15[###]
Shen	100, 4[$]		63	92		6					12
	100, 4[$]		68	83		10					5
Vogl			30		23	0	0	54	RECIST	0/9/57/33	13

CP Child-Pugh classification of severity of cirrhosis A–C, *ECOG PS* Eastern Cooperative Oncology Group performance status 0–4, *RECIST* Response Evaluation Criteria in Solid Tumors (National Cancer Institute), *WHO* World Health Organization, *CR* complete response, *PR* partial response, *MR* minor response (WHO criteria only), *SD* stable disease, *PD* progression of disease, *OS* overall survival, *TACI* transarterial chemoinfusion, *cTACE* conventional transarterial chemoembolization (chemotherapy in K Lipiodol, ± gelfoam or permanent embolic), *TARE* transarterial radioembolization, *DEB-TACE* drug-eluting bead TACE, *RFA* radiofrequency ablation, *MWA* microwave ablation; *gem-cis* gemcitabine + cisplatin, *CS* case series, *CC* case/control, *RCS* retrospective analysis of prospectively gathered case series data, *TAG* tris-acryl gelatin microspheres, *PVA* polyvinyl alcohol microspheres

* Mean OS reported, not median

** Resections after transarterial therapy not censored from survival data

*** OS reported from time of diagnosis, not first treatment

[$] Subsequent to transarterial therapy

[$$] Concurrent with transarterial therapy

[#] Study combined patients with ICC and hepatic metastases from pancreatic carcinoma

[##] Authors defined hypervascularity by diagnostic CT or MR, not by angiography as is more typical in this literature

[###] Study combined patients with ICC and intrahepatic adenocarcinoma of unknown primary

European Association for the Study of the Liver (EASL) and modified Response Evaluation Criteria in Solid Tumors (mRECIST) systems were not explicitly used; however, these results would appear to correlate roughly with between 57 and 78 % complete response rates by these modern criteria. Median survival was 23 months from diagnosis. Two patients were downstaged to resection and were censored from the survival data. The authors did not separately report median survival from time of first TACE treatment [20].

Vogl et. al. recently published a series of 24 patients with either ICC or hepatic metastases of pancreatic adenocarcinoma treated with a dose-escalation protocol using gemcitabine as either TACI or TACE with a mean of 9 treatment sessions. TACE was performed with EmboCept degradable starch microspheres (PharmaCept GmbH, Berlin, Germany). The transarterial catheters were removed after each treatment session. Nine of 12 (75 %) TACI patients and 8/12 (67 %) TACE patients had ICC. In their study, WHO criteria were used to gauge imaging response to treatment. As is often the case after transarterial therapy, there were no complete or partial responses (disappearance of lesions or significant decrease in product of orthogonal tumor diameters, respectively) in either the TACE or TACI group. Nine of 12 (75 %) patients receiving TACI had SD, while 3/12 (25 %) had progression. In the TACE group, there were 11/12 (92 %) with SD and 1/12 (8 %) with progression. The mean time to progression was 4.2 months and 6.8 months in the TACI and TACE groups, respectively ($p < 0.01$). Mean survival from time of diagnosis was 13.5 months and 20.2 months in the TACI and TACE groups, respectively ($p < 0.01$) [14].

Herber et al. presented a series of 15 patients with unresectable ICC treated with a mean of 3.9 TACE treatments using mitomycin C in Lipiodol without particle embolization. RECIST criteria were assessed after three treatments: 1 patient had partial response, 9 patients had stable disease, and 5 progressed. Mean and median survival were 21.1 months and 16.3 months after first treatment, respectively. The authors noted mean survival in patients very large or miliary tumors was poorest, 3.4 months, whereas mean survival in patients with focal lesions in a single lobe was 27.5 months [21].

Gusani et al. published a retrospective review of 42 patients with ICC receiving transarterial gemcitabine, cisplatin, oxaliplatin, or gemcitabine with cisplatin, each followed by particle embolization with Embospheres (Biosphere Medical, Inc., Rockland, MA, USA). These investigators showed significantly improved median survival from time of first TACE with gemcitabine–cisplatin dual-agent therapy than with gemcitabine alone (13.8 vs. 6.3 months, $p = 0.0005$). A median of 3.5 TACE sessions per patient were administered. Twenty of 42 (48 %) patients showing SD by RECIST criteria after 3 treatments were found to have a median survival of 13.1 months, whereas 15/42 (36 %) with PD had a median survival of 6.9 months ($p = 0.017$). The investigators additionally noted that patients with peripheral tumors treated with TACE had median survival of 18.7 months, while those with central tumors survived a median of 8.2 months after TACE ($0 = 0.012$). There was no difference seen between patients with and without extrahepatic spread of disease at baseline [22].

Kim et al. published a series of 49 patients receiving either TACE, TACI, or both. Forty of 49 patients (82 %) were Child A, with the remainder being Child B. There were a median of 3 TACE or TACI treatments per patient. Twenty patients received TACE alone, 13 patients received TACI alone, and 16 patients received both TACE and TACI treatments. TACE was performed using cisplatin in Ethiodol followed by 1-mm-diameter gelfoam microsphere embolization of the vessel supplying the tumor. If no tumor hypervascularity was noted at angiography, chemoinfusion was performed without Ethiodol or gelfoam embolic. Median survival from time of first treatment was 10 months. Imaging assessment was performed a month after treatment. RECIST criteria were used with an additional category, tumor necrosis, added by the investigators characterized by lack of tumor enhancement. Ten of 49 patients (20 %) had RECIST PR, 17/49 (35 %) had tumor necrosis, 15/49 (31 %) had SD, and 7/49 (14 %) had PD. The authors defined clinical success as achievement of either RECIST PR or tumor necrosis on imaging follow-up, findings present in a total of 27/49 (55 %) patients. Student's t and Fischer exact tests were used with uni- and multivariate logistic regression analysis to compare rates of clinical success associated with the following factors: age; sex; child class; tumor size, type (peripheral or periductal-infiltrating), multiplicity and vascularity; prior radiation therapy; treatment group (TACE vs. TACI); and treatment frequency. Two of these variables, treatment modality and tumor vascularity, were found to be significant by univariate regression analysis: 15/20 patients (75 %) receiving TACE had clinical success versus 1/13 (8 %) receiving TACI ($p < 0.001$), and 26/36 patients (72 %) with hypervascular tumors had clinical success versus 1/13 (8 %) of those with hypovascular tumors ($p < 0.001$).With multivariate regression analysis, only tumor vascularity was found significantly related to clinical success (OR 31.2, $p = 0.002$).

Similar analysis was performed assessing these factors' impact on likelihood of dying during the study period. Tumor hypovascularity (OR = 10.6, $p < 0.001$), Child-Pugh class B (OR = 4.1, $p = 0.006$), and treatment with TACI (OR = 4.7, $p = 0.002$) were associated with decreased survival by univariate analysis. Tumor size of 8 cm or larger approached but did not reach significance (OR = 2.1, $p = 0.116$). By multivariate analysis,

hypovascularity (OR = 13.5, $p < 0.001$), and Child class B were again associated with decreased likelihood of survival (OR = 3.6, $p = 0.014$), but treatment group was not found to be significant. Large tumor size, though not found significantly related to survival by univariate analysis, did result in significantly decreased odds of survival by multivariate regression (OR = 2.6, $p = 0.048$) [15].

Park et al. retrospectively reviewed 155 patients with unresectable ICC, 72 of whom received a mean of 2.5 cTACE treatments and 83 of whom received best supportive care (BSC). TACE was performed as 2 mg/kg cisplatin via the lobar or proper hepatic artery over 15 min, followed by selective embolization of 3–10 mL of 1:1 cisplatin in Ethiodol, followed by embolization to stasis with 1-mm-diameter gelfoam sponge spheres. Overall survival was measured from time of diagnosis in both groups. Log-rank test was used with Student's *t* test or the Fischer exact test to identify demographic differences between the cTACE and BSC groups, to detect differential survival between these groups and to perform subgroup analyses of those with liver-only disease, extrahepatic disease, and those showing radiological response to treatment by RECIST criteria versus nonresponders. There were no significant differences between BSC and cTACE groups regarding age; sex; cancer stage; ECOG performance status (PS); tumor location, size, vascularity or multiplicity; or baseline bloodwork including white blood cell count, hemoglobin level, platelet count, serum albumin, total bilirubin, AST, ALT, or ALP (alkaline phosphatase). Median survival from diagnosis was 12.2 months with cTACE versus 3.3 months with BSC ($p < 0.001$). This difference was upheld in subanalysis of patients with disease confined to the liver (13.3 months with cTACE vs. 4 months with BSC, $p < 0.001$) and those with extrahepatic spread at baseline (11.3 months with cTACE vs. 3.2 months with BSC, $p < 0.001$). In those receiving cTACE, survival was longer among those demonstrating objective response (defined by the authors as RECIST PR or CR) than those who displayed none (22 months vs. 10.9 months, $p = 0.001$). Tumor response to treatment by RECIST criteria from CT scans obtained in 66/72 patients 1–3 months post-cTACE was 15/66 (23 %) PR, 44/66 (67 %) SD, and 7/66 (11 %) PD. ECOG PS; tumor stage, focality, lobar distribution and vascularity; and liver function or other serological characteristics were not found associated with differential survival, possibly, the authors suggested, due to power limitations from small sample size [23].

Kiefer et al. treated 62 patients with biopsy-proven ICC or adenocarcinoma of unknown primary compatible with pancreatobiliary origin thought to represent cholangiocarcinoma at 2 institutions with a mean of 2.7 cTACE sessions using identical TACE technique comprised of 100 mg cisplatin, 10 mg mitomycin C, and 50 mg doxorubicin 1:1 with Ethiodol followed by 0.2 mL of 150–250-micron-diameter spherical PVA particles (Contour SE, Natick, MA). The angiographic goal was stasis in the tumor vessel(s) with forward flow preserved in the infused segmental or lobar artery. Standard pre- and post-procedure medical care was provided. Survival and time to progression (TTP) were calculated for all patients and analyzed by subgroup for differences between pathologic groups. RECIST 1.0 was determined 1 month after completion of TACE. Forty-five of 62 patients had complete imaging follow-up. Five of 45 (11 %) demonstrated PR, 29/45 (64 %) had SD, and 11/45 (24 %) had PD. Three of 29 (10 %) patients with pathology-proven cholangiocarcinoma had PR, 19/29 (66 %) had SD, and 7 (24 %) had PD. In the adenocarcinoma of unknown primary group, there were 2 (13 %) PR, 10 (63 %) SD and 4 (25 %) PD. Median OS in the entire group was 20 and 15 months from time of diagnosis and first TACE, respectively. There was no difference in median survival from diagnosis or first TACE between patients with ICC or adenocarcinoma of unknown primary (20 and 15 months vs. 19 and 14 months, $p = 0.88$ and 0.51). Prior systemic chemotherapy was associated with prolonged survival (28 vs. 16 months, $p = 0.02$). The absence of extrahepatic disease trended toward prolonged survival but was not statistically significant (18 vs. 13 months, $p = 0.12$). Median TTP in any organ was 8 months regardless of the presence or absence of extrahepatic disease. Eighty-two percent of patients had no change in ECOG PS after treatment. The remainder were evenly split between improvement and worsening PS after treatment. Twenty-one patients had abnormally elevated serum CA 19–9 levels at baseline (> 37 U/mL); 4/21 (20 %) normalized after TACE (CR), 8/21 (40 %) declined by 50 % (PR), 7/21 (35 %) changed < 50 % (SD), and 2/21 (10 %) increased > 50 % (PD). A statistical comparison of CA 19–9 levels and survival was not performed. The parity of survival and imaging response to treatment between those with ICC and adenocarcinoma of unknown primary was cited by the authors to support the hypothesis that the two cohorts represent well-differentiated and poorly differentiated ends of a common spectrum of ICC malignancy [24].

Shen et al. published the first dedicated study of adjuvant transarterial therapy after surgical resection with curative intent. In a retrospective series of 125 patients having undergone hepatectomy for ICC, 53/125 (42 %) received TACI or TACE 1.5–2.0 months after resection at the discretion of the surgeon. TACI with fluorouracil 500 mg or a mix of carboplatin 100 mg, epirubicin 20 mg, and hydroxycamptothecin 10 mg was performed via the proper hepatic artery in all patients. For patients with angiographic evidence of recurrent tumor, 3–5 mL of iodinated oil was added to the chemotherapeutic agents. Demographics, OS, and PFS were compared between groups with the chi-squared test. There were no statistically significant

differences in these baseline characteristics between those patients receiving transarterial therapy and those who did not. There also were no differences between the two groups regarding age, amount of blood transfused during hepatectomy, adequacy of resection margin, TNM staging, or serum CA 19–9. Demographic variables that did differ between treatment groups were sex and the presence of microvascular invasion. Of those receiving TACE or TACI, only 8/38 (21 %) were women, while 29/72 (40 %) were women in the historical control ($p = 0.002$). Twenty-three of 53 (43 %) patients treated with TACE/TACI had microvascular invasion, compared to only 15/72 (21 %) of those who did not receive adjunct therapy ($p = 0.007$). One-, 3-, and 5-year recurrence-free survival periods were not different between the two groups ($p = 0.659$), but the TACE/TACI group did experience slightly better overall survival (69.8, 37.7 and 28.3 % vs. 54.2, 25.0 and 20.8 %, $p = 0.045$). Early recurrence was found in 54/125 (43 %) of patients, 27/53 (51 %) of TACE/TACI patients and 27/72 (38 %) of non-TACE/TACI patients. Subgroup analysis showed that median OS in those with early recurrence was 12 months in the TACE/TACI group versus 5 months in the nonadjuvant cohort ($p < 0.001$). The only demographic variable differing between groups in the subgroups analysis was age: only 10/27 (37 %) of patients in the adjuvant therapy group were 54 years old or older versus 18/27 (67 %) of those not receiving adjuvant treatments. It is possible that this difference confounded improved OS in the TACE/TACI group in the setting of early recurrence. It should also be noted that since TACE was provided if and only if tumor recurrence (i.e., hypervascularity or blush) was seen at angiography, patients in the early recurrence subgroup analysis who received adjuvant transarterial therapy would all have received TACE and not TACI. In this manner, the improved OS in the treatment group may at least in part reflect a response to embolic therapy and/or hypervascular tumor histology and should probably not be construed as a response to transarterial chemoinfusion. These factors may have, to a lesser extent, also accounted for the slightly improved OS with TACE/TACE in the entire study population [16].

Vogl et al. treated 115 patients with a mean 7.1 cTACE treatments at 4-week intervals using 4 chemotherapeutic regimens consisting of mitomycin C, gemcitabine, both mitomycin and gemcitabine, or gemcitabine, mitomycin, and cisplatin. Chemotherapy was administered in Lipiodol and followed by 200-micron degradable starch microspheres. The authors compared several patient factors' effects on survival using the log-rank test: Child-Pugh class; tumor variables of number, localization, and vascularity; TACE regimen; and imaging response to treatment by RECIST using noncontrast MRI every month during the first 3 months of treatment. Tumor hypervascularity was defined as the presence of demonstrable tumor vessels by angiography and localization of Lipiodol solely within tumor by noncontrast CT performed 4–6 h after each embolization. Tumor hypovascularity was defined as the presence of only faintly demonstrable tumor vessels on angiography and only scant uptake of Lipiodol by the tumor by post-procedure noncontrast CT. Patients were excluded if they had cardiac or pulmonary failure, tumor burden >70 %, Child C cirrhosis, portal vein thrombosis, extrahepatic metastases, serum bilirubin >3.0 mg/dL, albumin <2.0 mg/dL, creatinine >2.0 mg/dL, or Karnofsky PS of 70 % or less. Ten of 115 patients (9 %) had a PR by RECIST criteria, 66/115 (57 %) had SD, and 39/115 (34 %) had PD. Maximal imaging response was typically seen 3 months after first treatment. The median survival from first treatment in the entire group was 13 months. There was no survival difference between the different chemotherapeutic protocols or based on tumor focality or localization. Factors found to favor increased survival included the following: Child class A (21.7 months median OS vs. 11.0 months for child B, $p < 0.001$) and tumor hypervascularity (24.0 vs. 9.0 months median OS, $p < 0.001$). PD by RECIST at initial imaging follow-up was associated with shorter survival (9.0 vs. 17.0 months for SD, $p < 0.001$, and 25.2 months for PR) [25].

Knuppel et al. described retrospective review of 195 patients treated at the gastrointestinal clinic at a single center during a 6-year period with surgical resection, systemic chemotherapy, photodynamic therapy, and/or TACE. These investigators, however, failed to separate patients with ICC from those with extrahepatic cholangiocarcinoma in their analyses, so interpretation of their results is difficult [26].

3.2 Drug-eluting Bead TACE

Table 2 summarizes results of these DEB-TACE and TARE studies. In 2010, Lammer et al. reported results of a randomized, controlled, multicenter trial of doxorubicin-DEB-TACE versus cTACE for HCC. They found that in addition to experiencing fewer chemotherapy-associated side effects, patients with more advanced disease, such as those with ECOG 1 or poorer performance status, Child B cirrhosis or bilobar or recurrent disease, had significantly greater objective response to treatment by EASL criteria at 6 months than those treated with cTACE [27]. Based on these results and other trials suggesting safety and efficacy of DEB-TACE for HCC, investigators have more recently studied the DEB-TACE for ICC.

Aliberti et al. described a cohort study comparing 11 patients receiving doxorubicin-DEB-TACE (DEBDOX) with 9 patients receiving systemic chemotherapy comprised of mainly fluorouracil, cisplatin, or doxorubicin regimens.

Table 2 Results of these DEB-TACE and TARE studies

Primary author	Year	Study type	Type of treatment	Number of patients	Mean or median # of Rx sessions	Noncirrhotic or CP A	ECOG 0	ECOG 1	ECOG 2+	Prior chemotherapy (%)	Prior external beam radiotherapy (%)	Prior thermal ablation (%)
Aliberti	2008	CC	doxorubicin-DEB-TACE	11	2.6					+	+	+
			systemic fluorouracil	9						+	+	+
Poggi	2009	CC	systemic oxaliplatin and gemcitabine	11		91			0			
			oxaliplatin DEB-TACE + systemic gem-ox	9	3.3	100			0			
Kuhlmann	2012	CC	irinotecan DEB-TACE	26	1.6	100	62	35	4	19	4	
			cTACE: mitomycin C + gelfoam	10	1.4	100	70	30	0	20	10	
			systemic oxaliplatin and gemcitabine	31		100	65	32	3	0	3	
Schiffman	2011	RCS	irinotecan and/or doxorubicin-DEB-TACE	24	1.75		38	50	4	58-80, 33[$$]		12, 12[$]
Ibrahim	2008	CS	TARE: glass microspheres	24	2		42	50	8	29		
Saxena	2010	CS	TARE: resin microspheres	25	1		60	28	12	72		8
Hoffman	2012	CS	TARE: resin microspheres	33	1		52	21	27	82	3	6
Rafi	2012	RCS	TARE: resin microspheres	19	1.6		5	74	21	100	0	0

(continued)

Table 2 (continued)

Primary author	Prior surgical resection (%)	Mean or median tumor size (cm)	Single tumor (%)	Peripheral morphology (%)	Unilobar disease (%)	Extrahepatic (%)	Portal vein thrombus (%)	Approx % liver vol replaced by tumor (< 25/ < 50/< 75)	Treatment response imaging criteria	RECIST or WHO imaging assessment of response to treatment at 3 months or earliest post-treatment interval (% CR/ PR/(MR)/SD/PD)	Median OS (months)
Aliberti	[+]	6.5							RECIST	9/82/0/0	13
	[+]	6.5									7
Poggi						0			RECIST	0/0/73/27	20
	22[$]					0			RECIST	0/44/56/0	30**
Kuhlmann	4					42			RECIST	0/3/42/50	11.7
	0					40			RECIST	0/12.5/12.5/75	5.7
	23					90			RECIST	0/26/45/29[++]	11.0[++]
Schiffman	29, 12[$]	11.5	12			42		38/46/17	RECIST, mRECIST	4/4/83/8, 4/75/12/8	17.5** ***
Ibrahim	4[$]		46	71	33	33	38	83/13/4	WHO, EASL	0/27/68/5, 9/77/[+++]/[+++]	14.9**
Saxena	40			60	20	48	0	40/60/0	RECIST	0/26/48/22	9.3**
Hoffman	36		30	36	36	24	0	76/24/0	RECIST	0/36/52/15	22
Rafi	0		32		58	58			RECIST	0/11/68/21	11.5

CP Child-Pugh classification of severity of cirrhosis A–C, *ECOG PS* Eastern Cooperative Oncology Group performance status 0–4, *RECIST* Response Evaluation Criteria in Solid Tumors (National Cancer Institute); *WHO* World Health Organization, *CR* complete response, *PR* partial response, *MR* minor response (WHO criteria only), *SD* stable disease, *PD* progression of disease, *OS* overall survival, *TACI* transarterial chemoinfusion, *cTACE* conventional transarterial chemoembolization (chemotherapy in Lipiodol, ± gelfoam or permanent embolic), *TARE* transarterial radioembolization, *DEB-TACE* = drug-eluting bead TACE, *RFA* radiofrequency ablation, *MWA* microwave ablation, *gem-cis* gemcitabine + cisplatin, *CS* case series, *CC* case/control, *RCS* retrospective analysis of prospectively gathered case series data, *TAG* tris-acryl gelatin microspheres, *PVA* polyvinyl alcohol microspheres, *mRECIST* modified RECIST criteria for measuring enhancing tumor, *EASL* European Association for the Study of the Liver criteria for measuring enhancing tumor

* Mean OS reported, not median

** Resections after transarterial therapy not censored from survival data

*** OS reported from time of diagnosis, not first treatment

[$] Subsequent to transarterial therapy

[$$] Concurrent with transarterial therapy

[#] Study combined patients with ICC and hepatic metastases from pancreatic carcinoma

[##] All patients by this finding deemed to have recurrence post-resection

[###] Study combined patients with ICC and intrahepatic adenocarcinoma of unknown primary

[+] All patients had prior chemotherapy and/or surgery, specific quantities not specified

[++] 55 % of systemic therapy patients had extrahepatic cholangiocarcioma or gallbladder carcinoma

[+++] SD and PD not reported

Patients receiving doxorubicin-DEBDOX had a median survival of 13 months versus a median survival of 7 months in the systemic chemotherapy group. Imaging response to treatment was assessed by RECIST criteria from CT datasets at 3 months after initial treatment. In the treatment group, there was 1 CR (9 %), and 9 PRs (82 %), with a mean 45 % reduction in tumor volume demonstrated by 3D CT. The authors also assessed quality of life using the Edmonton Symptom Assessment System (ESAS) for patient receiving DEBDOX. Ten of 11 DEBDOX patients reported improved quality of life by ESAS scores. ESAS scores and imaging assessment were not performed for the group of patients receiving systemic chemotherapy and/or palliative care alone. There was no demographic comparison of the two historical groups [28].

Poggi et.al reported a study in which 9 patients with unresectable ICC received a mean of 3.3 rounds of TACE with oxaliplatin-eluting microspheres (OEM-TACE) using HepaSpheres/QuadraSpheres followed upon completion of the final TACE session by standard systemic chemotherapy. This experimental group was then compared with a historical control cohort of 11 patients receiving only systemic oxaliplatin and gemcitabine chemotherapy. In the experimental group, 50–100-micron-diameter Hepaspheres were mixed with 50 mg oxaliplatin and diluted in isosmolar contrast to a total volume of 30 mL. TACE was performed to stasis as selectively within the right or left hepatic artery branch as possible. Eight of 11 patients (73 %) receiving only systemic chemotherapy were found to have PD by RECIST criteria after 3 and 6 cycles of chemotherapy, and 3/11 (27 %) had SD. Response 3 months after the first TACE session in the experimental group was PR in 4/9 (44 %) and SD in 5/9 (56 %). Three patients who had a PR were able to undergo curative resection. The fourth patient showing PR was not eligible for resection but had an FDG-PET scan showing the absence of metabolic activity in the treated lesion. Progression-free survival (PFS) and OS were compared between groups using the log-rank test. The OEM-TACE group had median PFS and OS from first treatment of 8.4 and 30 months, respectively, versus 2.9 and 12.7 months in the systemic chemotherapy cohort ($p < 0.004$) [29].

Kuhlmann et al. retrospectively compared 26 patients who received a mean of 1.6 irinotecan DEB-TACE treatments (iDEB-TACE or DEBIRI) with 10 patients receiving mitomycin and gelfoam cTACE and 31 patients receiving systemic chemotherapy comprised of oxaliplatin and gemcitabine. Treatments did not overlap. Of note, 23/26 (88 %) iDEB-TACE patients and 9/10 (90 %) cTACE patients had ICC; and 3/26 (12 %) and 1/10 (10 %), respectively, had carcinoma of the gallbladder while only 14/31 (45 %) systemic chemotherapy patients had ICC, 10/31 (32 %) had gallbladder cancer, and 7/31 (23 %) had extrahepatic cholangiocarcinoma. Patients treated with iDEB-TACE had a median age of 67 versus 62 and 63 years for cTACE and systemic chemotherapy groups, respectively. Patients receiving TACE therapies had approximately even amounts of extrahepatic disease and liver-only disease, while those receiving systemic chemotherapy mostly had extrahepatic spread (28/31, 90 %). Rates of prior surgery and endoscopic stenting were slightly higher in the chemotherapy group, perhaps reflecting the variety of tumors treated in this group. Imaging assessment of the iDEB-TACE group with RECIST criteria 8 weeks after the first treatment revealed 1/26 (4 %) PR, 11/26 (42 %) SD, and 13/26 (50 %) PD (1 patient was lost to follow-up). Response in the cTACE group was 1/10 (10 %) PR, 1/10 (10 %) SD, and 6/10 PD (2 patients died before re-staging) while response in the systemic chemotherapy group was 8/31 (26 %) PR, 14/31 (45 %) SD, and 9/31 (29 %) PD. Median OS was 11.7 months for the iDEB-TACE group, 5.7 months for the cTACE group, and 11.0 months for those receiving systemic chemotherapy. Statistical analysis between groups was not performed [30].

Schiffman et al. described a retrospective review of prospectively gathered data on 24 patients with unresectable ICC entered into the International Bead Registry receiving a mean of 1.75 treatments with either irinotecan (35 treatments) or doxorubicin (7 treatments) DEB-TACE with LC Beads (DC Beads as marketed outside the United States). Median irinotecan dose per treatment was 75 mg (40–100 mg range). Doxorubicin dose was always 150 mg per treatment. The size of the beads used was usually 100–300 micron (71 % of cases), with the remainder of cases using either 300–500-micron beads or 100–300 followed by 300–500-micron beads. In only 1 case (2 %) were 500–700-micron beads used. Complete stasis of the infused arteries was reported in 46 % of cases, with near stasis reported in 33 % and partial stasis reported in 21 %. Treatment was lobar in 88 % of cases and segmental or subsegmental in 12 %. Tumor response to treatment at 3 months by RECIST criteria was 1/24 (4 %) CR, 1/24 (4 %) PR, 20/24 (83 %) SD, and 2/24 (8 %) PD. Response by mRECIST was 1/24 (4 %) CR, 18/24 (75 %) PR, 3/24 (12 %) SD, and 2/24 (8 %) PD. Median OS was 17.5 months from time of diagnosis. Three patients were downstaged to resection and radiofrequency ablation (RFA). The authors did not report the time between diagnosis and treatment or factors associated with prolonged survival [31].

3.3 Transarterial Radioembolization

Ibrahim et al. published a prospective single-arm series of 24 patients treated with a mean of 2.0 treatments of glass TARE. The median OS from time of initial TARE for the

entire cohort was 14.9 months. One patient of 24 (4 %) was downstaged to resection. The log-rank test was used to assess differences in survival based on a variety of baseline patient characteristics. Factors associated with improved survival were intact ECOG PS 0 (median OS 31.8 months vs. 6.1 months for ECOG PS 1 and 1.0 months for PS 2, $p < 0.0001$), the absence of portal vein thrombus (median OS 31.8 months vs. 5.7 months with PVT, $p < 0.0003$), peripheral (versus periductal infiltrative) tumor type (median OS 31.8 months for peripheral tumors vs. 5.7 months for infiltrative, $p < 0.0005$) and the absence of prior systemic chemotherapy (4.4 months vs. 31.8 months, $p = 0.0274$). The presence of a solitary intrahepatic tumor (14.9 months vs. 5.7 months, $p = 0.1826$) and the absence of extrahepatic disease (31.8 months vs. 6.1 months, $p = 0.3493$) trended toward improved survival but did not reach statistical significance. Imaging assessment of response to treatment was obtained in 22 of 24 (92 %) patients using both WHO and EASL criteria. Response by WHO criteria was PR 6/22 (27 %), SD 15/22 (68 %), and PD 1/22 (5 %). Response by EASL was CR 2/22 (9 %) and PR 17/22 (77). Nineteen of 22 patients showed an objective response to treatment, defined by the authors as any measurable decrease in tumor size [32].

Saxena et al. reported a retrospective series of 25 patients treated with ^{90}Y resin microspheres with a median survival from time of treatment of 9.3 months. Patients with bilobar disease had both lobes treated in a single session when feasible. Patient characteristics associated with differential survival were assessed, with the log-rank test and categorical variables assessed with chi-squared or Fischer's exact test, as appropriate. With univariate analysis, the authors found peripheral tumor type (median OS 18.3 months vs. infiltrative 4.5 months, $p = 0.004$) and ECOG PS 0 (18.3 months vs. 2.4 months for PS > 0, $p < 0.001$) as being significantly associated with prolonged survival. The absence of extrahepatic disease trended toward but did not achieve statistical significance (16.3 vs. 4.8 months, $p = 0.140$). Variables that were not shown to affect survival included age, sex, prior chemotherapy, tumor burden (<25 % vs. 25–50 %), time between diagnosis and treatment, and unilobar versus bilobar disease. The authors suggested the lack of significant difference in survival associated with these variables might be due to small sample size. Imaging response by RECIST at 1 and 3 months for the remaining 23 patients was 6/23 (26 %) PR, 11/23 (48 %) SD, and 5/23 (22 %) PD. One patient with PR was downstaged to resection [33].

Hoffman et al. reported a retrospective series in which they administered a mean of 1.0 treatments of resin-based TARE to 33 patients with unresectable ICC. Patients were a mean of 21.2 months from date of diagnosis when they underwent TARE. Median OS from TARE and from time of diagnosis were 22.0 and 43.7 months, respectively. Differences in survival between patient groups were assessed with the log-rank test. Factors associated with prolonged survival included ECOG PS 0 (29.4 months from treatment vs. 10.0 months for PS 1 and 5.1 months for PS 2, $p < 0.001$), response by RECIST criteria (35.3 months for PR vs. 17.7 SD and 5.7 PD, $p < 0.001$), and tumor burden <25 % (26.7 vs. 6.0 months if 26–50 % burden, $p < 0.001$). Decrease in CA 19–9 levels after treatment trended toward but did not reach statistical significance (29.4 vs. 10.0 months, $p = 0.29$). The presence or absence of prior chemotherapy or surgery did not significantly affect survival. By RECIST at 3 months from treatment, there were 12/33 PR, 17/33 SD, and 5/13 PD [34].

Rafi et al. prospectively collected data including survival and RECIST response in 19 patients receiving a mean of 1.6 treatments with resin microsphere TARE after having progressed on systemic chemotherapy. The investigators reported median survival of 11.5 months from first treatment and 25.1 months from diagnosis. Log-rank test, independent *t* test and chi-squared test were used to identify significant patient variables affecting survival. The only variable these authors found to prolong survival was prior TACE (22.1 vs. 11.5 months, $p = 0.047$). The authors speculated that since all patients having received prior TACE also had an ECOG PS of 1, whereas 4 of 19 patients in the study had ECOG PS of 2, the apparent difference made by prior TACE might have been confounded by better PS in this group. Other variables were analyzed but did not reach statistical significance. These included ECOG performance status, the presence of extrahepatic disease, multifocality of intrahepatic tumor, tumor size, unilobar versus bilobar tumor distribution, RECIST response, and change in serum bilirubin or AST from baseline. The investigators hypothesized that small sample size may have contributed to their results. They did not publish demographic data on peripheral versus infiltrative tumor histology. RECIST response assessed 3 months post-TARE was PR 2/19 (11 %), SD 13/19 (68 %), and PD 4/19 (21 %) [35].

4 Complications

Since its inception, the rationale for transarterial oncologic intervention has been the promise of equal or greater efficacy with fewer side effects than available systemic alternatives. As such, a brief review of the toxicity profile of state-of-the-art systemic chemotherapy at the time of this publication may provide the best frame of reference from which to interpret the toxicity profiles of the transarterial therapies detailed below. By way of reference, in their recent landmark paper describing dual-agent cisplatin-gemcitabine systemic chemotherapy, Valle et al. reported Common

Terminology Criteria for Adverse Events (CTCAE) 3.0 grade 3 or 4 toxicities in 140/198 patients (71 %) receiving the dual-agent regimen [36]. Unless otherwise specified, complications reviewed below are grade 3, 4, or 5.

4.1 Conventional TACE and TACI

There were no procedure-related complications reported in Tanaka et al.'s original series of 11 patients treated with TACI port placement. One of the 11 patients (9 %) developed hearing loss and weakness. There was 1 case of pancytopenia (9 %) and 2 cases of cholangitis (18 %) [19].

Five of 17 patients (29 %) treated by Burger et al. experienced self-limited post-embolization symptoms: nausea, vomiting, diarrhea, hypertension, tachycardia, and/or right upper quadrant abdominal pain which did not require prolonged hospitalization or significant further treatment. One patient (6 %) with grade 3 esophageal varices and large tumor suffered massive upper gastrointestinal hemorrhage and died 11 days post-treatment. The authors cautioned against treating large tumors in patients with decompensated cirrhosis. One patient (6 %) experienced severe right upper quadrant pain thought to be due to chemical cholecystitis or acute post-embolization syndrome that resolved with patient-controlled analgesia and intravenous fluids. One patient (6 %) developed ascites, mild jaundice, and left rib pain that resolved after 2 weeks with paracentesis of 3 L and cox-2 inhibitors [20].

In their report of 12 patients treated with gemcitabine TACI, Vogl et al. described 1 case (8.3 %) of pulmonary edema requiring intubation. The maximum-tolerated dose (MTD) in their dose-escalation protocol was reached due to WHO grade 3 myelosuppression in 2 of 3 patients at the 1600-mg/m^2 dose group. In the report of 12 patients treated with gemcitabine-starch microsphere TACE by the same authors, there was no severe adverse event. MTD was reached due to WHO grade 3 myelosuppression in 2 of 3 patients at 2,000 mg/m^2 [14].

Herber et al. reported post-embolization symptoms including right upper quadrant abdominal pain, nausea, and/or vomiting in 6/15 (40 %) of patients resolving with minimal medical therapy (minor, Class B). There was one case (6.7 %) of nontarget Lipiodol embolization leading to gastric ulceration requiring 7 days of intravenous proton pump inhibitor (PPI) therapy and 1 case (6.7 %) of anaphylaxis from iodinated contrast material requiring ICU care (each major, Class D). Two cases of severe hepatic arterial spasm resolved with catheter withdrawal from the artery and sublingual nitroglycerin (minor, class B) [21].

Gusani et al. reported CTCAE grade 4 toxicity in 2 of 42 patients (4.8 %): acute myocardial infarction resolving with percutaneous coronary intervention and abscess leading to sepsis and grade 4 thrombocytopenia requiring percutaneous drainage and prolonged hospitalization. Five additional patients (11.9 %) developed grade 3 adverse events (AEs). One patient developed mild respiratory distress from oversedation, 2 developed hyperbilirubinemia and 2 developed thrombocytopenia. Grade 1 and 2 AEs were seen in 7 (16.7 %) and 9 (21.4 %) of patients, respectively. These included elevations in serum bilirubin and creatinine, thrombocytopenia, hyperglycemia, hypertension, pulmonary edema, and pancreatitis. Nearly all patients experienced some degree of post-embolization syndrome [22].

Kim et al. reported nausea, vomiting, and/or fever compatible with post-embolization syndrome in most patients. One patient (2.0 %) with bilioenteric anastomosis and persistent fevers 34 days after treatment required percutaneous drainage, hospitalization, and antibiotic therapy for hepatic abscess [15].

Park et al. reported 9/72 (13 %) grade 3 or higher cases of hematological toxicity to their cisplatin cTACE therapy, 3/72 (4 %) being anemia, 6/72 (8 %) thrombocytopenia, 1/72 (1 %) neutropenia, and 1/72 (1 %) elevation in INR. There was 17/72 (24 %) nonhematological CTCAE grade 3 or higher toxicities: 2/72 (3 %) AST elevation, 1/72 (1 %) ALT elevation, 2/72 (3 %), alk. phos. elevation, 11/72 (15 %) bilirubin elevation, 5/72 (7 %) albumin decrease, 3/72 (4 %) pain, and 1/72 (1 %) nausea. There were no deaths within 30 days of treatment [23].

Kiefer et al. evaluated toxicity associated with their treatments according to CTCAE 3.0 criteria. Median hospital length of stay was one day. Post-embolization syndrome, defined as CTCAE grade 1 or greater pain, nausea, vomiting or fever, was experienced after 65 % of TACE procedures but was generally mild. Major complications occurred in 5 of 165 treatments (3 %). They included pulmonary edema and myocardial infarct on post-procedure day 2 (grade 4), readmission for management of severe post-embolization syndrome, readmission for hyperglycemia, and acute renal failure from dehydration [24].

Shen et al. reported nausea and/or vomiting in 25/53 (47 %) patients, abdominal pain in 19/53 (36 %), and fever in 6/53 (11 %). They did not quantify with WHO or CTCAE criteria but reported no severe complications such as liver or kidney failure or bone marrow suppression [16].

In their report of Lipiodol and starch microsphere multidrug TACE in 115 patients, Vogl et al. reported 15 patients (13.0 %) had post-embolization symptoms of pain, nausea, and vomiting requiring 2–7 days of hospital treatment. No major complications were reported [25].

Knuppel et al. did not report on complications in their retrospective review of patients receiving surgery, systemic chemotherapy, photodynamic therapy, and/or TACE [26].

4.2 Drug-eluting Bead TACE

Aliberti et al. reported hepatic abscess in one of 20 patients (5.0 %) treated with DEBDOX-TACE. Almost all TACE treatments (27/29, 93 %) were associated with WHO grade 2 nausea and vomiting within 12 h of treatment. Right upper quadrant pain resolving after an average of 10 h and neoplastic fever beginning 72 h and lasting an average of 2 days occurred after 29 of 29 treatments (100 %) [28].

Poggi et al. compared frequencies of CTCAE 3.0-graded adverse events in the OEM-TACE-systemic chemotherapy group versus AEs in the systemic chemotherapy-only group. Pain was a common complaint in both groups, with all grades of pain occurring in 42 % of OEM-TACE patients versus 25 % of systemic only patients, although 9 % of TACE patients suffered grade 3 pain versus none of the receiving only systemic chemotherapy ($p = 0.042$). Nausea and vomiting, however, were much more common in patients receiving only systemic chemotherapy (72 % all grades and 16 % grade 3) than in the TACE group (30 % all grades and no grade 3; $p < 0.001$). Mild and severe asthenia, peripheral neuropathy, and leukopenia were all significantly more frequent in the systemic chemotherapy-only group than in the TACE group: grade 1–2 asthenia 25 versus 3 % and grade 3 asthenia 9 versus 0 %, peripheral neuropathy 40 versus 4 % and 16 versus 0 %, and leukopenia 25 versus 4 % and 9 versus 0 %. Cholangitis was more common in the TACE group: 7 and 1 % versus 0 and 0 %. Mild transaminitis was also more frequent in the TACE group: 30 versus 16 %. There was no grade 3 transaminitis in either group [29].

In their comparison of systemic chemotherapy, cTACE and DEB-TACE, Kuhlmann et al. reported 1 death from cholangitis in each of the cTACE and iDEB-TACE groups (10 and 4 %, respectively). In each case, the patient had a disrupted sphincter of Oddi with a biliary stent. The patient in the cTACE group who died of cholangiosepsis also suffered a pulmonary embolism. One patient in the cTACE group died of liver failure associated with bacterial peritonitis 14 days after treatment. Three patients died (10 %) of treatment-related complications in the systemic chemotherapy group, 2 of cholangitis and 1 from tumor rupture. There were no other CTCAE grade 3 or 4 adverse events in the cTACE group. There were 2 liver abscesses and 1 empyema requiring drainage in the iDEB-TACE group. The empyema was thought by the authors to be related to biliary leak. Post-embolization pain was worse in the DEB-TACE group than in the cTACE group, with 7/26 (27 %) of DEB-TACE patients experiencing grade 3 or 4 pain but no 3 or 4 pain in the cTACE group. Overall, there were 11/26 (42 %) grade 3 or higher adverse events in the DEB-TACE group, 3/10 (30 %) grade 3 or higher AEs in the cTACE group, and 23/30 (77 %) grade 3 or greater AEs in the systemic chemotherapy group. Hematological AEs accounted for 17 of 23 AEs in patients receiving systemic chemotherapy, a rate of 57 %. Specific grade 3 or greater AEs in the chemotherapy group were leukocytopenia 5/30 (16 %), febrile neutropenia 2/30 (7 %), thrombocytopenia 7/30 (23 %), anemia 3/30 (10 %), and peripheral neuropathy 6/30 (19 %) [30].

Schiffman et al. reported grade 3 or higher adverse events in 4/24 (17 %) of patients treated with iDEB-TACE. One patient (4 %) with 50–75 % liver volume replacement by tumor died 12 days after treatment from hepatorenal syndrome. One patient (4 %) developed sepsis related to his chemoinfusion port. Two patients (8 %) developed self-limited grade 3 hepatic insufficiency [31].

4.3 Transarterial Radioembolization

Ibrahim et al. reported delivering a median transarterial radiation dose to liver of 105.5 Gy. Despite this tumoricidal dose, there were only 5/24 (21 %) grade 3 laboratory toxicities of liver function: 4/24 (17 %) hypoalbuminemia and 1/24 (4 %) hyperbilirubinemia. There were no treatment-related grade 4 hepatic toxicities and no deaths. One patient developed a gastroduodenal ulcer refractory to medical management requiring surgical resection. Eighteen of 24 patients (75 %) complained of fatigue, 9/24 (38 %) of abdominal pain, 4/24 (17 %) of nausea or vomiting, and 2/24 (8 %) of anorexia. The authors did not report what percentage of these was grade 3 versus lower grades. Median dose to lungs was 4.6 Gy per treatment and 8.4 Gy total, well below the generally accepted limits of 30 Gy/dose and 50 Gy cumulatively [32].

Saxena et al. reported serologic grade 3 liver toxicity in 3/25 (12 %) patients, 2 (8 %) with hypoalbuminemia, and 2 (4 %) with elevated alk. phos. No other chemical toxicities were observed. One patient suffered a duodenal ulcer that responded to medical therapy. Clinical toxicities not reported by grade included fatigue in 16/25 (64 %), self-limited abdominal pain in 10/25 (40 %), nausea or vomiting in 6/24 (25 %), anorexia in 4/25 (16 %), and shortness of breath in 2/25 (8 %) [33].

Hoffman et al. likewise reported no RILD, despite delivering a median activity of 1.54 GBq per TARE session. The authors described no deaths and reported finding no clinically relevant acute or delayed toxicities during follow-up. This seems to suggest that toxicities they reported were minor, although no CTCAE grades were provided. The investigators reported some degree of toxicity as follows: 23/33 (70 %) hyperbilirubinemia, 18/33 (54 %) AST elevation, 11/33 (33 %) ALT elevation, 16/33

Table 3 Results of thermal ablation investigations

	Yu	Kim	Xu	Fu
Year	2011	2011	2012	2012
Study type	case series	case series	case series prospective data	case series
Treatment type	MWA	RFA	RFA or MWA	RFA
# of Patients	15	13	18	17
Mean or median # of treatment sessions	2.5	1.3	1.1	1.1
Noncirrhotic or CP A (%)	93		89	82
Single tumor (%)	67	76	72	76
Mean or median tumor size (cm)	3.2	3.0	2.8	4.4
Extrahepatic disease (%)	0		0	70
Median OS (months from treatment)	10	38.5	30.3, 62.5*	33

RFA radiofrequency ablation, *MWA* microwave ablation, *OS* overall survival
* Median OS in patients with primary, rather than recurrent ICC

(48 %) LDH elevation, 28/33 (85 %) abdominal pain, 20/33 (61 %) nausea, and 9/33 (27 %) vomiting [34].

Rafi et al. reported no treatment-related deaths, no grade 4 toxicities, and no cases of GI ulceration. Two of 19 (11 %) patients had grade 3 toxicity; however, the exact toxicity they experienced was not described. Grade 1–3 toxicities were categorized as gastrointestinal 6/19 (32 %), hematological 1/19 (5 %), hepatic 6/19 (32 %), and other 4/19 (21 %) [35].

5 Image-Guided Percutaneous Thermal Ablation

Recently, several groups of investigators have reported promising early results from percutaneous thermal (radiofrequency or microwave) ablation of small- to moderate-sized, usually solitary, ICCs in patients who are considered poor candidates for surgical resection or who have recurrent disease after resection with curative intent. Table 3 summarizes results of these thermal ablation investigations.

The first moderate-sized series to prove safety and efficacy of microwave ablation for ICC was published in 2011 by Yu et al. who described sonographically guided percutaneous microwave ablation of 24 tumors in 15 patients with biopsy-proven ICC. With a mean of 2.5 treatment sessions per patient, this group achieved median OS of 10 months, similar to many prior series published for transarterial therapies. Their major complication rate was 20 %, with abscesses requiring drainage occurring in 2 patients at 3 and 13 months after ablation, and needle tract seeding occurring in 1 of these patients. The authors speculate that their relatively low survival and high complication rates reflected patient selection factors, such as 25 % of cases involving tumors adjacent critical structures such as bowel or central vessels [37]. Studies yielding more impressive results followed shortly.

Kim et al. described a series of 13 patients with 17 tumors treated with percutaneous RFA for with median OS and PFS of 38.5 and 32.2 months, respectively. Mean maximum tumor diameter was 3.0 cm. Technical success, defined as complete tumor ablation by contrast CT or MRI 1 month after treatment, was achieved in 15/17 patients. The 2 patients in whom residual tumor was found at 1 month had tumors measuring 7 and 8 cm diameter. One patient (8 %) developed a liver abscess that was treated with antibiotics and percutaneous drainage. This same patient died of sepsis 3.3 months after the ablation. No other severe complications occurred [38].

Fu et al. published a retrospective study of RFA treatment for 26 ICC tumors in 17 patients ranging from 2.1 to 6.9 cm diameter (median 4.4 cm) with technical success in 25/26 (96 %) cases at 1 month follow-up. The 1 case in 26 with local recurrence at 1 month was successfully treated with a second ablation. Median OS was 33 months, and recurrence-free survival was 17 months. Univariate regression analysis revealed pathologic tumor grade ($p = 0.033$) was associated with decreased overall survival. One patient (4 %) suffered a major complication: dyspnea resolved after thoracentesis [39].

Xu et al. reported retrospectively evaluated results of prospectively gathered data on percutaneous RFA or microwave ablation for 25 ICC tumors in 18 patients, 8 with primary and 10 with lesions recurring post-resection. Technical success was achieved in 23/25 (92 %) tumors ranging in size from 0.7 to 4.3 cm diameter, with a mean tumor maximum diameter of 2.8 cm. Residual viable tumor was seen 1 month after treatment for 2/25 tumors with diameters of 6.4 and 6.9 cm. Recurrence after surgical resection was associated with decreased overall survival by univariate regression analysis. OS for the entire cohort was 30.3 % at 60 months; however, for those without prior resection (primary rather than recurrent), OS was 62.5 % at 60 months ($p = 0.001$ by univariate regression analysis).

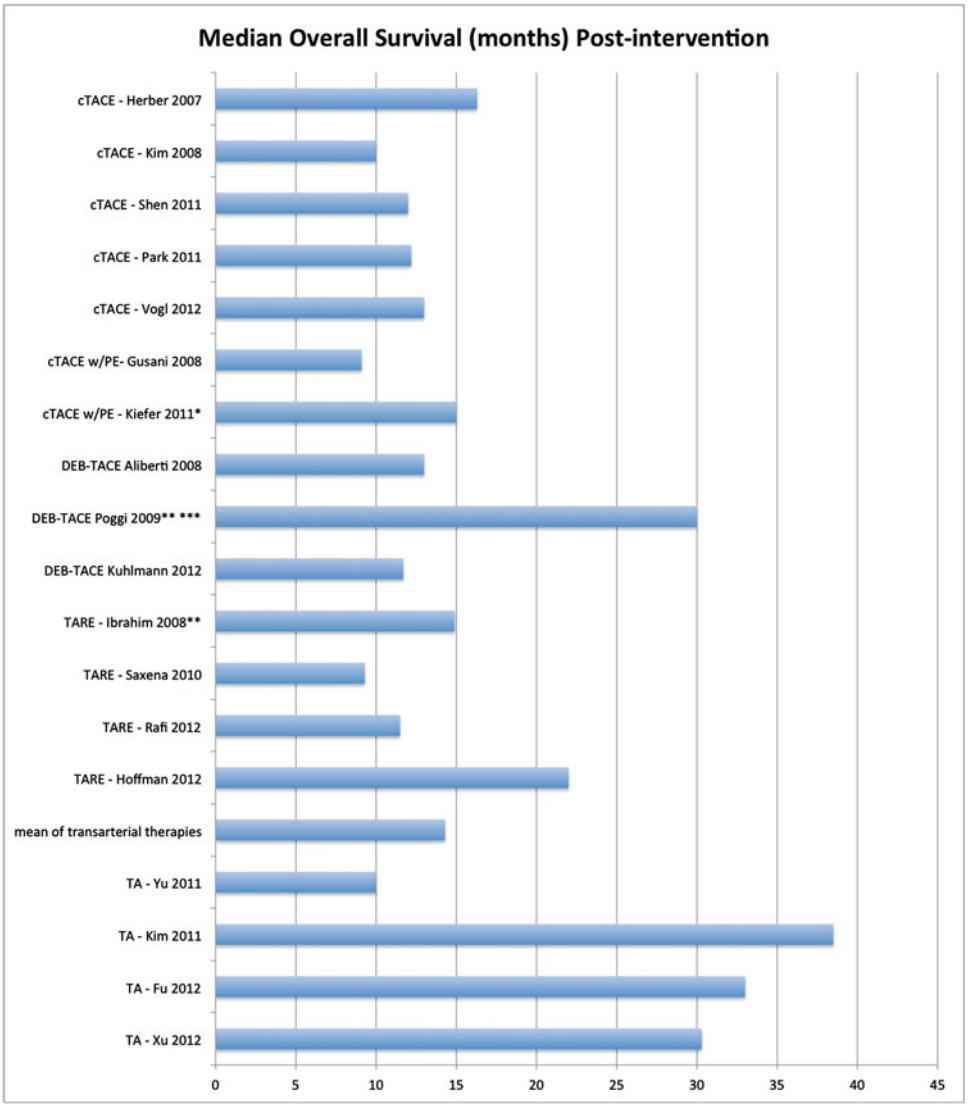

Fig. 3 Median overall survival post-intervention by studies cited in this chapter. *cTACE* conventional transarterial chemoembolization with temporary embolic (Lipiodol and/or gelfoam or starch microspheres), *cTACE w/ PE* cTACE with permanent embolic material (tris-acryl gelatin or polyvinyl alcohol); *DEB-TACE* drug-eluting bead TACE, *TARE* transarterial radioembolization with ^{90}Y-bearing microspheres, *TA* thermal ablation (radiofrequency or microwave), *patients included ICC and adenocarcinoma of unknown primary, **includes patients downstaged to resection, ***patients received oxaliplatin DEB-TACE followed by systemic gemcitabine + oxaliplatin

There was 1 major complication (6 %), in which a fever of suspected infectious etiology responded to antibiotic therapy [40].

6 Conclusion

Inoperable ICC continues to have a dismal prognosis. Originally developed for patients with unresectable HCC, the application of transarterial therapies has been shown by numerous small- and medium-sized series to prolong survival in patients with unresectable ICC well beyond a year after intervention. A review of the current literature reveals several interesting observations in the interventional management of this disease. The parity of response to treatment and of survival outcomes between patients with biopsy-proven cholangiocarcinoma and intrahepatic adenocarcinoma of unknown primary in the study by Kiefer et al. supports the hypothesis that the latter entity may in fact be poorly differentiated cholangiocarcinoma.

While treatment with state-of-the-art dual-agent systemic chemotherapy is associated with overall survival of less than 12 months [36], average OS after transarterial therapy based on the studies reviewed here is over 14 months (Fig. 3). DEB-TACE and TARE are newer transarterial treatment modalities that may further maximize treatment effect while minimizing morbidity from systemic exposure. Of particular interest is the study by Poggi et al. combining DEB-TACE with dual-agent systemic chemotherapy to achieve a median OS of 30 months. Further investigation into the potential

Table 4 Factors related to prolonged survival

Primary author	Year	Rx type	N Pts	Child-Pugh A	ECOG PS 0	Prior chemotherapy	Prior TACE	Primary (vs. recurrent post-op)	Peripheral morphology	Small tumor size	Low tumor grade	Tumor burden < 25 %	Absence of portal thrombus	Hypervascularity	Embolic therapy	Gem-cis dual-agent cTACE	(+) RECIST response
Vogl	2006	TACI/ TACE	12												<0.01		
Gusani	2008	TACE	42						0.012							0.0005	0.017 SD vs. PD
Kim	2008	TACE/ TACI	42	0.014						0.048				<0.001	0.002*		
Ibrahim	2008	TARE	24		<0.0001	0.0274**		<0.0005					<0.0003				
Saxena	2010	TARE	25		<0.001*				0.004*								
Park	2011	TACE vs. BSC	75														0.001 OR vs. SD or PD
Kiefer	2011	TACE	62			0.02											
Shen	2011	TACI/ TACE vs. BSC***	53												0.045		
Vogl	2012	TACE	115	<0.001										<0.001			<0.001 OR or SD vs. PD
Hoffman	2012	TARE	33		<0.001							<0.001					<0.001 OR or SD vs. PD
Rafi	2012	TARE	19				0.047										
Fu	2012	RFA	17								0.033*						
Xu	2012	RFA and MWA	18					0.001*									

TACI transarterial chemoinfusion, *TACE* transarterial chemoembolization, *BSC* best supportive care, *systemic* systemic chemotherapy, *TARE* transarterial radioembolization, *DEB-TACE* drug-eluting bead TACE, *RFA* radiofrequency ablation, *MWA* microwave ablation, *RECIST* Response Evaluation Criteria in Solid Tumors (copyright National Cancer Institute), *CR* RECIST complete response, *PR* partial response, *SD* stable disease, *PD* progression of disease, *OR* sum of CR + PR, *gem-cis* gemcitabine + cisplatin

All *p* values by multivariate regression analysis unless indicated by *, in which case univariate analysis was used

** Prior chemotherapy negatively associated with prolonged survival

*** All patients with recurrence post-resection, variables not found associated with differential survival: solitary tumors and extrahepatic disease

benefit of combined systemic and transarterial therapy is needed to confirm these encouraging initial findings.

Research to date suggests that patient factors associated with prolonged survival include the absence of cirrhosis or the presence of no worse than Child A cirrhosis, normal or near normal (0–1) ECOG performance status, peripheral (rather than periductal) tumor type, tumor hypervascularity, small tumor size, low tumor grade, low tumor burden, the absence of portal thrombus, prior TACE and RECIST imaging evidence of stable disease or response to treatment (Table 4). Several studies have found that transarterial chemoembolic therapy is more effective than transarterial chemoinfusion alone for unresectable ICC; however, no study has been conducted to evaluate whether this difference between TACE and TACI persists in the subpopulation of hypovascular tumors. One study, by Gusani et al., found that, just as has been confirmed for systemic chemotherapy, dual-agent conventional TACE with gemcitabine and cisplatin was more effective than single-agent cTACE. The presence of extrahepatic disease has not been found significantly to impact survival, confirming the high mortality of the primary disease.

Early results of percutaneous RFA and microwave ablation for selected patients with small-to-moderate-sized unresectable ICC are promising. Three recent studies of patients receiving thermal ablation each reported median OS periods of over 30 months post-treatment. One of these studies, by Xu et al., noted that excluding patients treated for recurrence post-resection yielded a median OS of 62.5 months, survival similar to that often cited for resection itself. Prospective studies of transarterial and percutaneous ablative therapies are needed.

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