

The role of interventional radiology in the treatment of intrahepatic cholangiocarcinoma

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Abstract Intrahepatic cholangiocarcinoma (ICC) is the second most common primary hepatic malignancy after hepatocellular carcinoma. Complete surgical resection remains the only potentially curative option for patients with ICC. However, until now, early diagnosis with potential surgical intervention has been the exception rather than the rule with only 30% of patients qualifying for attempted surgical cure. Many patients are unresectable because of disease stage, anatomic conditions, medical comorbidities, and small future remnant liver. Interventional radiology procedures are available for these types of patients with intra-arterial therapies and/or ablative treatments both for curative and for palliative treatment. The goals of interventional therapy are to control local tumor growth, to relieve symptoms, and to improve and preserve quality of life. The choice of treatment depends largely on tumor extent and patient performance. No randomized studies exist to compare treatments. The present review describes the current evidence of the interventional treatments in the management of the ICC.

Moreover, interventional procedures available to increase the future liver reserve before surgery were analyzed.

Keywords Intrahepatic cholangiocarcinoma · Interventional radiology · Intra-arterial therapies · Ablative treatments · Palliative treatment · Radioembolization

Introduction

Cholangiocarcinoma (CC) is the second most frequent type of primary liver cancer, and it represents 3% of all gastrointestinal neoplasms [1].

Cholangiocarcinoma (CC) can arise from every point of the biliary system: intrahepatic (ICC) or extrahepatic (ECC); the extrahepatic CC is classified as perihilar (pCC) or distal CCA (dCC).

Approximately up to 10% of all cholangiocarcinomas are intrahepatic, whereas 50–60% are pCC and the remaining involve the distal bile duct (dCC) [2].

The majority of CCs occur in the absence of an evident chronic liver disease or other risk factors. However, the most relevant risk factors for CC are: primary sclerosing cholangitis (PSC), liver flukes, HCV-related and HBV-related liver diseases. ICC occurs in patients with chronic liver disease and/or cirrhosis more often than pCC and dCC [3, 4].

On the basis of the macroscopic appearance, the ICC can present in three different patterns of growth: mass-forming (MF-ICC), periductal infiltrating (PI-ICC), and intraductal growing (IG-ICC). The mass-forming type represents the most frequent macroscopic presentation of ICC (>90%) [5, 6].

Treatment for cholangiocarcinoma depends on the clinical condition of the patient and the stage of disease. Surgery with complete resection represents the only

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treatment for CC with potential curative intent [7]. Survival after resection mainly depends on the presence of tumor-negative margins, absence of vascular invasion and lymph node metastasis, and adequate functional liver remnant [8]. Overall, 5-year survival after resection has ranges 22–44% for ICC; 1–41% for pCC, and 27–37% for dCC [9]. Unfortunately, the majority of patients develop recurrence following surgical resection. Liver transplantation has been associated with rapid tumor recurrence and low survival rates (10–25%) and is not recommended as a treatment for CC [10].

Many patients that are technically resectable cannot undergo surgery as a result of medical comorbidities, disease stage, or small future liver remnant (FLR) [6].

The prognosis of patients with advanced ICC is poor, with an estimated median survival of 3–8 months [11, 12]. Intra-arterial therapies (IAT) and/or ablative treatments (AT) are available with the potential for cure or for palliation, to relieve symptoms, and to improve and/or preserve quality of life.

IAT for primary liver tumors are efficient, safe and can improve survival [13–15]. IAT include bland embolization (TAE), transarterial chemoembolization (TACE), drug-

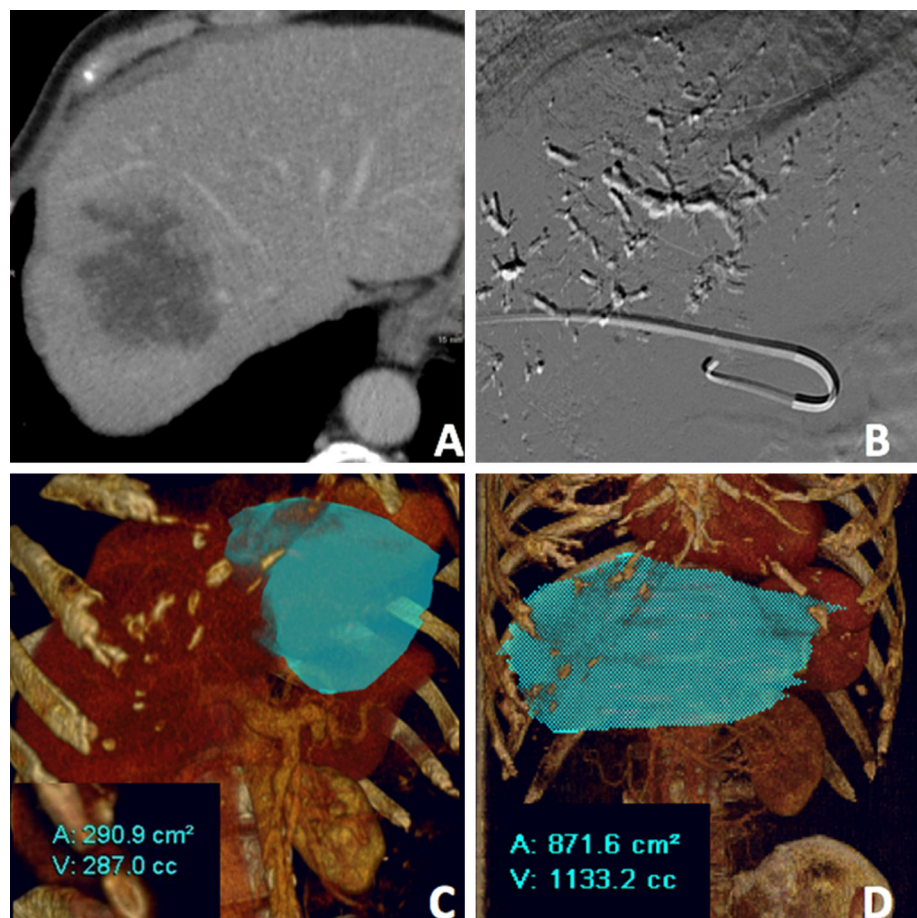
eluting bead TACE (DEB-TACE) or radioembolization (yttrium-90). No statistically significant difference has been found in small RCT evaluating these therapies in the management of HCC. To date, there is no RCT comparing these different IAT for ICC [15].

Thermal ablation has been used as a curative option for HCC and is currently recommended instead of surgery for small HCC that can be treated with margins. However, the efficacy of thermal ablation for ICC lacks sufficient evidence [16].

Percutaneous image-guided thermal ablation using MWA or RFA is safe and effective in the treatment of ICC. It may be an alternative treatment approach in some cases of ICC, particularly for smaller tumors that can be treated with margins in patients that are not candidates for surgery. It has satisfactory local therapeutic efficacy, low complication rate, and acceptable survival [17].

The purpose of the present review is to describe the current evidence of the interventional treatments in the management of the intrahepatic cholangiocarcinoma. Moreover, we analyzed the interventional procedures used to increase the future liver reserve before surgery.

Fig. 1 CT scan reveals intrahepatic cholangiocarcinoma (a); a right portal vein embolization with *N*-butyl-cyanoacrylate was performed (b); the volume of left lobe was 290.9 cm³ (c) before surgery and 871.6 cm³ after surgery (d)



Materials and methods

Study selection

A systematic literature search was performed in PubMed, with the syntax interventional radiology and intrahepatic cholangiocarcinoma; intrahepatic cholangiocarcinoma and portal vein embolization; intrahepatic cholangiocarcinoma and intra-arterial therapies or IAT or transarterial chemoembolization or TACE, drug-eluting bead TACE or DEB-TACE or radioembolization or yttrium-90; intrahepatic cholangiocarcinoma and ablative treatments or radiofrequency ablation or RFA or microwave ablation or MWA, including only studies published in English from January 2005 to June 2016. All titles and abstracts of identified studies in the initial search were screened to select those reporting interventional radiology treatments in patients with unresectable intrahepatic cholangiocarcinoma.

We also included studies in which tumors were treated simultaneously with percutaneous ablation and transarterial embolization. We identified additional studies through manual search of the primary studies references, review articles, and key journals. We excluded papers that included data reported previously.

The primary endpoint was to investigate safety and complications of these techniques. Secondary endpoint was to present the current status of interventional radiology in the treatment of unresectable intrahepatic cholangiocarcinoma.

The following variables were extracted, where available, from the included articles: number of patients; number of lesions and their diameter; number of sessions of treatment; complications; mean follow-up; technical and clinical success. Median survival was calculated.

Clinical evidence

Portal vein embolization and radioembolization to bridge for surgery

Only a minority of patients with ICC are candidates for surgical resection [2]. In general, a FLR of 20–25% is recommended after surgery, although higher volumes are needed for patients with compromised liver function [18]. Percutaneous portal vein embolization can induce contralateral lobe hypertrophy and can therefore reduce the risks of postoperative liver insufficiency and increase the number of patients who may be eligible for surgical resection [19]. One of the major disadvantages of portal vein embolization is the time required to induce hypertrophy, which can be more than 1 month. This delay before surgery may allow for interval tumor growth, which could

theoretically worsen prognosis or exclude patients from surgical resection [20].

In most cases, a right portal vein embolization is needed (Fig. 1a–d). Left portal vein embolization is rarely performed because a left trisegmentectomy typically results in a FLR of greater than 30%. After access into the portal vein is obtained, a variety of embolic agents have been used, including particles, coils, and liquid adhesives (i.e., n-butyl cyanoacrylate or Onyx) [21].

Interestingly, postembolization syndrome is uncommon compared with the incidence observed in transarterial embolization. Complications are rare and include issues at the access site such as hematoma, bleeding and rarely pneumothorax. Portal vein thrombosis can also occur; therefore, the ipsilateral (to the resection site) approach is favored so as not to compromise FLR [22].

Hypertrophy starts immediately and is often seen on imaging 1 month after the procedure. The degree of hypertrophy varies significantly based on different published studies [18].

Presently, unilobar radioembolization or selective internal radiation therapy (SIRT) with Yttrium-90 has been described as technique to afford a significant hypertrophy of the contralateral liver lobe [23]. This finding is relatively recent and has the potential of increasing resectability rates.

Apart from few case reports, two institutions have reported their experiences with radioembolization in downstaging [24, 25].

Rayar et al. [25] reported successful downstaging to resection with radioembolization and chemotherapy in eight patients with initially unresectable ICC. R0 resections were achieved in all patients, with a median of six resected segments. Mouli et al. [24] reported successful downstaging to resection in 5/46 patients with unresectable ICC and successful liver transplantation in one patient.

Recently, some studies have compared the hypertrophy seen with portal vein embolization to that seen with yttrium-90 (⁹⁰Y) radioembolization. Seemingly, portal vein embolization tends to induce more significant contralateral hypertrophy at an early time point compared with radioembolization [26, 27]. Adverse events following radioembolization were fatigue, abdominal pain, nausea, vomiting, fever/chills, weight loss, hyperbilirubinemia, diarrhea and pseudoaneurysm at the puncture site [27].

Intra-arterial therapies

The role of intra-arterial therapy (IAT) for hepatocellular carcinoma is well established, with two randomized trials demonstrating a survival benefit over best supportive care [13, 14].

Table 1 Table reporting studies about TACE treatment of ICC since 2007 to date

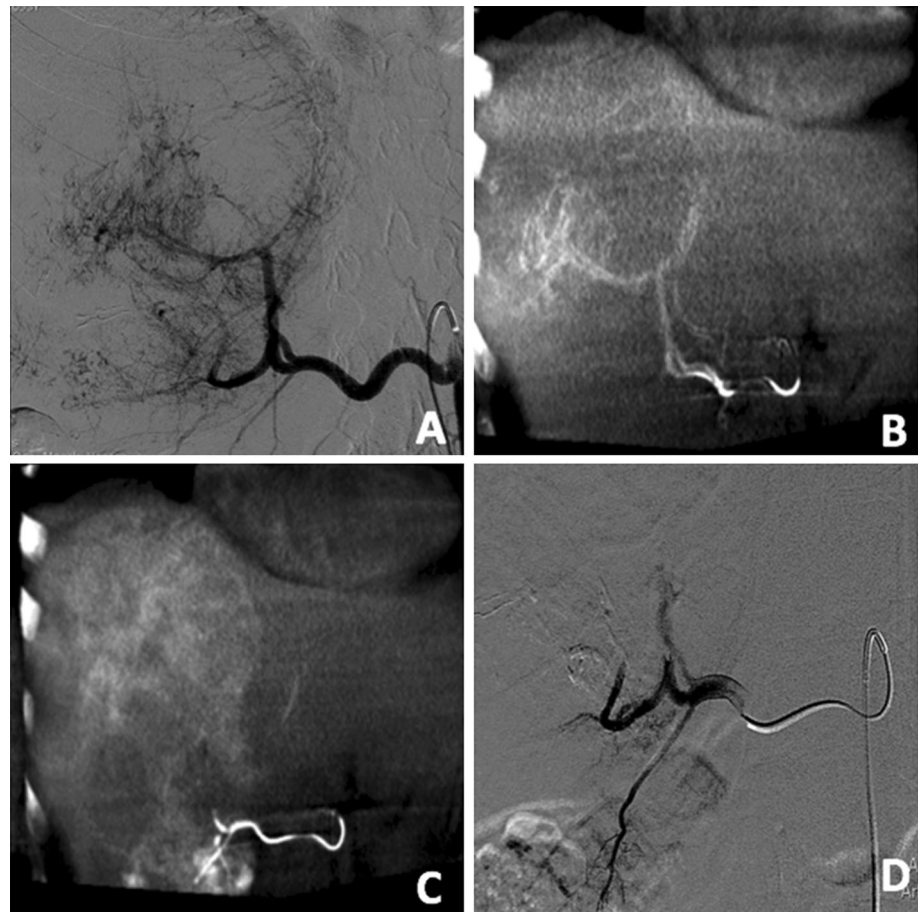
References	No. pts	No. lesions, diameter	Chemotherapy type	Sessions of treatment (range)	Technical success	Clinical success	Follow up (months)	Median survival (months)		Complications
								From diagnosis	From procedure	
Burger et al. [11]	17	1–3; 9 × 7 cm average	Cisplatin, doxorubicin, mitomycin-C	1–3	N.S.	NO RECIST 8/17 necrosis 75% 13/17 significant tumor necrosis 3/17 decrease in tumor size	16	23	N.S.	9/18 no side effects 7/18 minor side effects (nausea, vomiting, diarrhea, hypertension, tachycardia, and right upper quadrant pain) 1/18 death
Herber et al. [28]	15	1–10; 10.8 ± 4.6 cm	Mitomycin C	1–15	15/15	RECIST 9/15 SD 1/15 PR (decrease >30%) 4/15 PD (increase >20%)	18	16.3	16.3	6/15 mild effects (pain, vomiting) 2/15 severe hepatic artery spasm 1/15 lipiodol gastric displacement 1/15 anaphylactic shock
Gusani et al. [29]	42	1; 9.8 cm	Gemcitabine, gemcitabine then cisplatin, gemcitabine then oxaliplatin, gemcitabine plus cisplatin	1–16	N.S.	RECIST 20/42 SD 15/42 PD 7/42 not evaluable	6 years	N.S.	9.1	2/42 grade 4 AE: myocardial infarction, abscess 5/42: grade 3 AE: Over sedation, hyperbilirubinemia, thrombocytopenia 16/42 grade 1–2 AE: elevated total bilirubin, elevated creatinine, thrombocytopenia, hyperglycemia, hypertension, pulmonary edema, pancreatitis
Kim et al. [30]	49	N.S.; 8.1 ± 3.2 cm	TACE (n = 13) TACE (n = 21) TACE and TACE (n = 15); using cisplatin	1–17	49/49	RECIST + non-necrosis RECIST (%) 27/49 clinical response 10/27 reduction size <30% 17/27 successful necrosis 15/49 SD 7/49 PD	8	12	10	1/42 abscess N.S./42 nausea, vomiting, fever

Table 1 continued

References	No. pts	No. lesions, diameter	Chemotherapy type	Sessions of treatment (range)	Technical success	Clinical success	Follow up (months)	Median survival (months)		Complications
								From diagnosis	From procedure	
Kiefer et al. [31]	62	N.S.; 7.8 cm	Cisplatin, doxorubicin, and mitomycin-C	1–4	N.S.	RECIST 5/62 11% PR 29/62 64% SD 11/62 24% PD 17/62 lost at follow-up	65	20	15	3% procedures major complication (pulmonary edema, pulmonary infarct, severe postembolization syndrome, hyperglycemia, acute renal failure) 65% procedures: mild postembolization syndrome
Andrašina et al. [32]	17	N.S.	Cisplatin; 5-FU	1	N.S.	N.S.	N.S.	25.2	N.S.	N.S./17 postembolization syndrome
Park et al. [33]	72	1 to >5; 8.1 ± 3.4 cm	Cisplatin (+geifoam)	1–17	N.S.	RECIST 15/72 PR 44/72 SD 7/72 PD 6/72 lost at follow up	80	N.S.	12.2	26/72 severe toxicities (hematological toxicities, increased bilirubin, pain, nausea, increased AST-ALT, decreased albumin)
Vogl et al. [34]	115	1 to >5; N.S.	Varied, including mitomycin-C, gemcitabine and cisplatin	3–30	N.S.	RECIST 10/115 8.7% PR 66/115 57.4% SD 39/115 33.9% PD	100	N.S.	13	No major complications 15/115 abdominal pain, nausea and vomiting for 2–7 days
Scheuermann et al. [35]	32	1–3; 2–18 cm	Mitomycin C	1–18	N.S.	N.S.	1–65	N.S.	11	2/32 hepatic artery dissection 1/32 massive ascites

N.S. not specified, CR complete response, PR partial response, SD stable disease, PD progressive disease, AE adverse event, TACE transcatheter arterial chemoembolization, TACI transcatheter arterial chemoinfusion

Fig. 2 Selective angiography shows intrahepatic voluminous tumor (a); dual phases CBCT shows feeding vessels (b) and intra-lesional vascularization (c), respectively; final angiography shows embolization of the lesion (d)



IAT can involve bland embolization (TAE), transarterial chemoembolization (TACE), drug-eluting bead TACE (DEB-TACE) or radioembolization (yttrium-90) and hepatic arterial infusion of chemotherapy (HAIC).

Because hepatocellular carcinoma is typically a very vascular tumor, IAT can take advantage of the fact that the majority of the tumor's blood supply comes from the hepatic artery compared with normal hepatocytes, which are primarily supplied by the portal vein [15]. In contrast, ICC is often more hypovascular in nature, potentially making IAT more technically challenging as well as possibly less effective [11].

All the reports known are small single-institution series [15]. In addition, the type of IAT utilized varied considerably from center to center, making interpretation of the data difficult and generalization of the findings limited.

Hyder et al. [15] stratified overall survival on the basis of type of tumor response considered (mRECIST or EASL criteria): complete or partial response and stable disease were 25–35 and 50–60%, respectively. Moreover, ECOG performance status was associated with outcome, as patients with worse ECOG status before IAT had worse results. Adverse effects associated with IAT were relatively

uncommon. Only 16 (8.1%) patients had a severe complication, including renal failure, hepatic failure, and liver abscess. Lastly, no statistical differences in overall survival were observed between the types of IAT utilized.

Transarterial chemoembolization (TACE)

Inclusion and exclusion criteria for chemoembolization in patients with ICC are similar to those for patients with hepatocellular carcinoma.

Patients undergoing chemoembolization should have adequate hepatic function (Child-Pugh Class A or B) and acceptable functional performance status [Eastern Cooperative Oncology Group (ECOG) 0–2]. In patients with elevated bilirubin levels, the possibility of biliary obstruction by the tumor should be considered. These cases represent a high-risk situation regarding postprocedural biliary infection. Techniques such as bowel preparation and prolonged antibiotic use have been employed in small case series [18].

In Table 1 [11, 28–35], we reported all published series of patients with inoperable intrahepatic cholangiocarcinoma treated with transarterial chemoembolization. These

Table 2 Table reporting studies about deb-TACE treatment of ICC since 2008 to date

References	No. pts	No. lesions, diameter (cm)	Chemotherapy type	Sessions of treatment	Technical success	Clinical success	Duration follow-up (months)	Median survival (months)		Complications
								From diagnosis	From procedure	
Aliberti et al. [40]	11	N.S.; 6.5	Doxorubicin/DEB	1-3 Tot = 29	100%	RECIST	3	N.S.	13	1/29 hepatic abscess 27/29 nausea and vomiting 29/29
						1/11 CR 9/11 PR				
Kuhlmann et al. [41]	26	N.S.	Irinotecan/DEB	1-3 Tot = 41	N.S.	Mean reduction volume: 45% (30-69%)	12	N.S.	11.7; 3.9 PFS	hypochoondrial pain 3/29 fever 18/26 pain 15/26 nausea 2/26 fever 2/26 hypertension 1/26 pleural empyema 2/26 liver abscess
						RECIST				
						1/26 PR 11/26 SD 13/26 PD				
Harder et al. [42]	13	N.S.	Irinotecan/DEB	Tot = 21	N.S.	RECIST	11	N.S.	8.6 PFS	10/13 right upper abdomen pain
Poggi et al. [43]	9	1-4; N.S.	Oxaliplatin/hepaSphere	1-7 Tot = 30	N.S.	RECIST	3; 35 median observational time	N.S.	30; 8.6 PFS	Abdominal pain, nausea and vomiting, asthemia, neuropathy, cholangitis, hypertensive crisis, elevated AST-ALT
						1/13 PR 8/13 SD 4/13 PD				
						RECIST 4/9 PR 5/9 SD				
Schiffman et al. [44]	24	1-25; 11.5	Irinotecan/DEB doxorubicin/DEB	1-3 Tot = 42	100%	RECIST	3-6-9/12; 13.6 median observational time	N.S.	17.5	63.6% minor complications 4/24 postembolization syndrome 1/24 pneumonia 2/24 arrial fibrillation 2/24 hepatic insufficiency 1/24 sepsis 1/24 death
						3 m: 1/24 CR 1/24 PR 20/24 SD 2/24 PD				
						6 m: 2/24 CR 3/24 PR 13/24 SD 2/24 PD				
						9-12 m: 1/24 CR 1/24 PR 13/24 SD 1/24 PD				

Pts patients, DEB drug-eluting beads, N.S. not specified, CR complete response, PR partial response, SD stable disease, PD progressive disease, PFS progression-free survival, m months

Table 3 Table reporting studies about radioembolization of ICC since 2008 to date

References	No. pts	No. lesions, diameter (cm)	Device	Sessions of treatment	Technical success	Clinical success	Follow up (months)	Median survival (months)		Complications
								From diagnosis	From procedure	
Ibrahim et al. [49]	24	11 Solitary lesions 13 Multifocal; N.S.	Glass microspheres	N.S.	N.S.	WHO 6/24 PR 15/24 SD 3/24 PD EASL 2/24 necrosis 100% 17/24: necrosis 77%	17.7	14.9	N.S.	3/24 grade 3 albumin toxicity 1/24 grade 3 bilirubin toxicity 18/24 fatigue 9/24 transient, vague abdominal pain 3/24 vomiting 2/24 anorexia 1/24 nausea 1/24 gastroduodenal ulcer 3/24 ascites 2/24 pleural effusions 64% fatigue 40% abdominal pain 8% grade 3 bilirubin and albumin toxicity 4% grade III alkaline phosphatase toxicity
Saxena et al. [50]	25	N.S.	Resin microspheres	N.S.	N.S.	RECIST 6/25 PR 11/25 SD 8/25 PD 2/25 died in 1 month	8.1	20.4	9.3	40% abdominal pain 23/33 bilirubin toxicity 28/33 abdominal pain 20/33 nausea 9/33 vomiting 2/40 acute radiation hepatitis 1/40 chronic radiation hepatitis prior to death 1/40 obstructive jaundice 6/40 fatigue (grade >2) 2/40 anorexia and weight loss (grade >2) 3/40 abdominal pain (grade >2)
Hoffmann et al. [51]	33	10 Solitary lesion 32 Multifocal; N.S.	Resin microspheres	1	N.S.	RECIST 12/33 PR 17/33 SD 5/33 PD after 3 months	13.5	43.7	22	23/33 bilirubin toxicity 28/33 abdominal pain 20/33 nausea 9/33 vomiting 2/40 acute radiation hepatitis 1/40 chronic radiation hepatitis prior to death 1/40 obstructive jaundice 6/40 fatigue (grade >2) 2/40 anorexia and weight loss (grade >2) 3/40 abdominal pain (grade >2)
Shridhar et al. [52]	40	N.S.	Glass microspheres	1	N.S.	N.S.	6	N.S.	7.4	2/40 acute radiation hepatitis 1/40 chronic radiation hepatitis prior to death 1/40 obstructive jaundice 6/40 fatigue (grade >2) 2/40 anorexia and weight loss (grade >2) 3/40 abdominal pain (grade >2)

Table 3 continued

References	No. pts	No. lesions, diameter (cm)	Device	Sessions of treatment	Technical success	Clinical success	Follow up (months)	Median survival (months)		Complications
								From diagnosis	From procedure	
Mouli et al. [24]	46	30 Solitary lesion 16 Multifocal; N.S.	Glass microspheres	Average 2: 14/46 1 tt, 8/46 2 tts, 24/46 ≥3 tts	N.S.	WHO 11/46 PR 33/46 SD 1/46 PD EASL 4/46 CR 28/46 PR 0/46 PD	29	N.S. 14.6 (solitary) 15.6 (peripheral) 6.1 (infiltrative)	25/46 fatigue 13/46 vague abdominal pain 6/46 nausea 4/46 vomiting 2/46 anorexia 4/46 grade 3 albumin toxicity 3/46 grade 3 bilirubin toxicity 1/46 gastroduodenal ulcer 7/46 ascites	
Rafi et al. [53]	19	6 Solitary lesion 13 Multifocal; 3 < 5 16 > 5	Resin microspheres	Average 1.3 ± 0.6 15/19 1 tt, 3/19 2tt, 1/19 3tt	N.S.	RECIST 2/19 PR 13/19 SD 4/19 PD	15	25.1 11.5	2/46 pleural effusions 6/19 abdominal pain 4/19 grade 1 fatigue	
Hyder et al. [15]	46	30 Solitary 16 Multifocal; 8, 1	N.S.	Average 1	N.S.	RECIST 61.5% PR 25.5% SD 13% PD EASL 34.6% PR 47.5% SD 17.9% PD	N.S.	N.S. 11.3	17% fatigue 12% abdominal pain 6% nausea 3% fever 2% jaundice Complications grouped with other modalities	
Camacho et al. [54]	21	N.S.; 48% < 5 52% > 5	Resin microspheres	N.S.	N.S.	mRECIST CR + PR 37.5%	N.S.	N.S. 16.3	N.S.	

N.S. not specified, PR partial response, SD stable disease, PD progressive disease, CR complete response, tt treatment, tts treatments

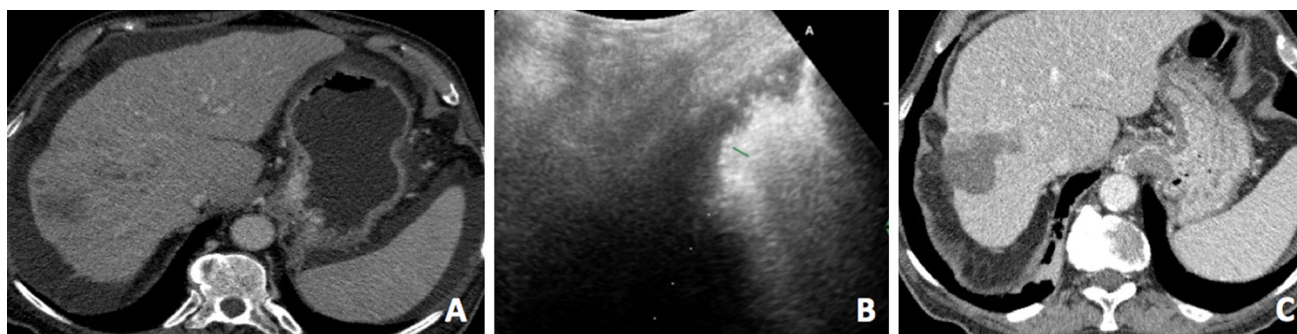


Fig. 3 CT scan shows intrahepatic cholangiocarcinoma (a); microwave thermal ablation performed under ultrasound guidance (b); CT scan performed during follow-up shows area of necrosis (c)

studies were very heterogeneous in regard to several variables (number and dimensions of the lesions), chemotherapeutic agent administered, number of treatment sessions. Most of the studies utilized modified RECIST criteria [36] to evaluate tumor response. Except for the series of Vogl et al. [34], all authors [11, 29–35] reported median survival from diagnosis.

Statistically significant survival benefit was registered for patients treated with TACE compared with patients receiving best supportive care (BSC), even in patients with extrahepatic metastases [31, 33, 34, 37].

Ray et al. [38] recently reported the results of a meta-analysis regarding chemoembolization for ICC. Over 16 studies, the overall median survival was 15.7 months from the date of diagnosis. Complete or partial response on follow-up imaging based on RECIST criteria was observed in 23% of patients. The overall severe complication rate was 19%, but there was a trend for even higher rates of severe complications (i.e., Common Terminology Criteria for Adverse Events grade 3 or higher) [39] in patients undergoing chemoembolization with irinotecan.

Drug-eluting beads-transarterial chemoembolization (DEB-TACE)

Chemoembolization with drug-eluting beads (DEB) combines the release of drugs from beads with a reduction of blood flow by embolization. Thus, beads with the ability to control drug release and drug dose offer the possibility to continuously apply the chemotherapeutic agent(s) into the tumor area [40].

Table 2 [40–44] reports all series published with patients with inoperable intrahepatic cholangiocarcinoma treated with DEB-TACE. The same considerations about the heterogeneity of the data available performed for patients treated with conventional TACE may be performed. Studies resulted were very heterogeneous for several variables (number and dimensions of the lesions),

chemotherapeutic agent administered, sessions of treatments.

Transarterial embolization (TAE)

Even in cases of “hypovascular tumours” on imaging, such as colorectal carcinoma and cholangiocarcinoma, the process of neovascularization from the arterial system is clearly demonstrated by injection of contrast medium via hepatic arterial catheterization while performing computed tomography (CT) angiography [45, 46] (Fig. 2a–d).

This technique is used preferentially over TACE in selected centers. In literature series of patients with HCC and neuroendocrine, liver metastases are more commonly reported [47, 48].

No randomized series on ICC are reported. A small number of patients ($n = 13$) treated with TAE were included in a multi-institutional analysis of patients with advanced ICC treated with IAT [15]. Median overall survival was 14 months, similar to that observed in the groups of patients treated with TACE, DEB-TACE, and ^{90}Y Radioembolization ($p = 0.46$).

^{90}Y radioembolization

^{90}Y radioembolization consists of the delivery of highly radioactive microspheres via the hepatic artery. Both resin (SIR- Sphere, Sirtex, Australia) and glass (TheraSphere, BTG, Canada) ^{90}Y microspheres have shown efficacy in patients with ICC.

Several studies regarding the use of radioembolization in ICC have been published in Table 3 [15, 24, 49–54]. Resin microspheres were the most used. In most cases, tumor was multifocal. Heterogeneity of results may be observed, and in particular RECIST criteria were the most used to evaluate treatment response; EASL and WHO criteria [55] were alternatively applied.

Table 4 Table reporting studies about thermoablation of ICC since 2005 to date

References	Method and approach	No. pts	No. of lesions	No. of lesion retreated	Tumor diameter range (cm)	Extrahepatic disease	Duration follow-up (months)	Technical success %	Technical effectiveness %	Median survival (months)	Local tumor progression	Complications	Observations
Chiou et al. [67]	RF	10, all primary	10	2	1.9–6.8	0	4–38	80	N.S.	14	1/10	10% (biloma)	N.S.
Carrafello et al. [68]	RF; TAE	6, all primary	6	3	1.0–5.8	0	13–21	N.S.	66	20	1/6	0	Combined RF + TAE
Kim et al. [69]	RF	13, all primary	17	2	0.8–8	15.4	3.3–82.1	88	88	38.5	6/17	6% (liver abscess)	N.S.
Giorgio et al. [70]	RF	10; 9 primary, 1 recurrent	12	2	2.4–7	N.S.	9–64	66.6	N.S.	1, 3, 5 Y OS 100%, 83.3%	1/10	0 (major) 30% (post ablation syndrome)	N.S.
Yu et al. [71]	MW	15, all primary	24	10	1.3–9.9	Excluded	4–31	87.5	91.7	10	6 dt 24	13.4% (2 abscess)	N.S.
Haidu et al. [72]	RF	11; 7 primary, 4 recurrent	36	2	2–10	27.3	12–81	100	92	60	3 dt 36	3%	N.S.
Xu et al. [17]	12 RF; 6 MW	18; 8 primary, 10 recurrent	25	1	0.7–4.3	Excluded	1.3–86.2	92	92	8.8	12 dt 16	5.5%	N.S.
Fu et al. [73]	RF	17; 7 primary, 10 recurrent	26	0	2.1–6.8	17.6	4–122	96.2	96.2	29	3/17	3.6%	N.S.
Butros et al. [74]	RF	7; 1 primary, 6 recurrent	9	0	1.3–3.3	0	31	89	100	38.5	1/9	0	N.S.
Yang et al. [75]	MW; TACE	26; 20 primary, 6 recurrent	39	0	2.5–6.5	Excluded	6–30	100	94	19.5	2	0	Combined MW + TACE

Pts patients, RF radiofrequency, N.S. not specified, TAE transcatheter arterial embolization, Y years, OS overall survival, MW microwave, TACE transarterial chemoembolization

When patients were stratified by response rate, the tumor response rate (using RECIST criteria) was found to be correlated with overall survival [51].

Response rates using modified RECIST criteria with specific assessment of delayed-phase imaging at 3 months were found to be an even stronger predictor of overall survival in another series [54]. Overall survival is higher than historical survival rates and shows similar survival to those patients treated with systemic chemotherapy and/or transarterial chemoembolization therapy. Complication profile is similar to that of other IAT [56].

Therefore, the use of Y-90 microspheres should be considered in the list of available treatment options for ICC.

Hepatic arterial infusion chemotherapy (HAIC)

Hepatic arterial infusion chemotherapy, via surgically inserted devices and, more recently, percutaneously implanted port-catheter systems by interventional specialists, proved to be an effective treatment option for selected patients with unresectable colorectal liver metastases [57]. In unresectable ICC, a few earlier studies suggested that HAIC is relatively safe and can improve survival [58–62]. These studies were underpowered due to the small number of patients and included a combination of ICC, HCC, and gallbladder cancer, making the interpretation of results difficult. In 2016, Konstantinidis et al. [63] performed a retrospective analysis of 236 unresectable patients with ICC treated with systemic chemotherapy and/or HAIC. They found that the group of patients with liver-confined disease ($n = 104$) who were treated with HAIC in addition to systemic chemotherapy ($n = 78$) experienced improved survival (30.8 months) in comparison with those who were treated with systemic chemotherapy only ($n = 26$; 18.4 months; $p < 0.001$). Currently, several phase 1 and 2 prospective trials investigating the effects of HAIC combined with systemic chemotherapy [64, 65] in patients with unresectable ICC are ongoing.

Ablation

Image-guided thermal ablation by means of radiofrequency ablation (RFA) or microwave ablation (MWA) has been proven to be a reasonable therapeutic option for the treatment of relatively small liver tumors, in selected patients (Fig. 3a–c). Advantages of image-guided local ablation include minimal invasiveness, easy performance, repeatability with relative low morbidity and diminished hospital stay that provides for a favorable cost-effectiveness or risk–benefit profile [66].

In suitable cases, thermal ablation can be used as a curative option for HCC [16]; however, the efficacy of thermal ablation for ICC lacks sufficient evidence.

ICC is nonencapsulated and always has a tendency to infiltrate adjacent tissues. It is the invasion of local and hepatic ducts by ICC that leads to the low rate of curative resection and the high recurrence rate after treatment. In general, it is necessary to completely destroy the tumor and an additional 0.5–1 cm of adjacent liver in an attempt to ensure a tumor-free margin [56].

On the basis of the data available in the literature in Table 4 [17, 67–75], RFA was the most used.

A recent meta-analysis established that RFA may be considered a locoregional treatment option that can prolong survival in patients with ICC who are ineligible for surgery [76].

Recently, Yang et al. [75] reported the first experience of 26 inoperable patients treated with percutaneous microwave ablation combined with simultaneous transarterial chemoembolization. Their results are encouraging with a high complete ablation rate without any major complication.

Conclusions

Currently multiple treatment options are available for inoperable ICC. The choice of treatment depends largely on tumor extent and patient performance status. No randomized studies exist to compare treatments; populations treated are very heterogeneous; the selection of therapy often varies from a center to another. Similarly to the approach used for hepatocellular carcinoma, thermal ablation is preferred when lesions are no more than 3 and size is suitable (ideally under 3 and arguably up to 5 cm). In conclusion, the current study provides important data demonstrating the feasibility, safety, and potential efficacy of interventional procedures for ICC, both in inoperable patients and in borderline ones to make them suitable for surgery.

The specific role of the interventional oncology in the management of ICC is growing. Larger studies with the help of international registries and ideally large, randomized, prospective trials are much needed to better demonstrate the benefits of local therapies in the management of ICC.

Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human or animal participants performed by any of the authors.

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