Chapter 18
Interventional Radiology Therapies for Intrahepatic Cholangiocarcinoma

Thomas J. An and Eric Wehrenberg-Klee

Abbreviations

CCA	Cholangiocarcinoma
cTACE	Conventional transarterial chemoembolization
DEB-TACE	Drug-eluting bead transarterial chemoembolization
ECOG	Eastern Cooperative Oncology Group
Gy	Gray
HCC	Hepatocellular carcinoma
iCCA	Intrahepatic cholangiocarcinoma
IR	Interventional radiology
LT	Liver transplantation
MAA	Macro-aggregated albumin
MELD	Model for End-Stage Liver Disease
MWA	Microwave ablation
RECIST	Response Evaluation Criteria in Solid Tumours
RFA	Radiofrequency ablation
TACE	Transarterial chemoembolization
TAE	Bland transarterial embolization
TARE	Transarterial radioembolization

T. J. An
Department of Radiology, Massachusetts General Hospital, Boston, MA, USA

E. Wehrenberg-Klee (✉)
Division of Interventional Radiology, Department of Radiology, Massachusetts General Hospital, Boston, MA, USA
e-mail: EWEHRENBERG-KLEE@PARTNERS.ORG

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Introduction

Cholangiocarcinoma (CCA) is the second most common primary hepatic malignancy after hepatocellular carcinoma. Classification of CCA is typically based on anatomic location, with extrahepatic CCA defined as involving the hilum (i.e., Klatskin tumor) or common bile duct and intrahepatic CCA (iCCA) defined as involving the second-order bile ducts [1]. Over 90% of CCAs are classified as extrahepatic, with the majority of those involving the hilum. The incidence of CCA appears to be increasing over the past several decades in the United States, with a disproportionate increase in particular of iCCA cases [2, 3]. Although many cases of CCA are sporadic, several risk factors for CCA development include chronic viral hepatitis, primary sclerosing cholangitis, and other chronic biliary tract disorders, including parasitic infections such as hepatobiliary flukes [1].

The prognosis for CCA is generally poor, with median 5-year survival of less than 10% [4]. Hepatic resection and liver transplantation (LT) are the only potentially curative options in the treatment of iCCA, with 5-year survival in patients undergoing surgical resection approximately 30% [5]. However, only approximately 30% of patients have resectable disease at the time of diagnosis. In addition, up to half of patients that undergo surgical resection develop recurrent disease, with the most common site of recurrence being within the remnant liver [6]. Most patients are asymptomatic during the initial stages of CCA, which makes early diagnosis and treatment extremely challenging. For patients with unresectable disease, systemic chemotherapy regimens are not very effective, with less than 1-year median overall survival even for standard-of-care chemotherapy with cisplatin and gemcitabine [7].

Interventional radiology (IR) offers several minimally invasive locoregional treatment options for unresectable iCCA and liver-dominant metastatic disease. The minimally invasive nature of interventional radiology procedures makes them well tolerated even in frail patients. Interventional radiology treatment modalities used in this context include thermal ablation, transarterial chemoembolization (TACE), and transarterial radioembolization (TARE). The aim of this chapter is to provide an overview of the different interventional radiology treatments for unresectable iCCA and summarize the available clinical data.

Thermal Ablation

Overview

Percutaneous thermal ablation is a minimally invasive procedure that uses extreme high or low temperatures to cause local tumor necrosis. Due to size constraints of ablation zones, thermal ablation is typically utilized in the setting of small- to medium-sized non-resectable tumors. Percutaneous placement of the ablation probes, which may be performed under CT or ultrasound guidance, makes the

procedure well-tolerated even in comorbid patients that are poor surgical candidates. Alternatively, ablation may also be performed concurrently with abdominal surgery through an open incision. Studies comparing percutaneous thermal ablative techniques to surgery for hepatic malignancies have demonstrated decreased morbidity and recovery times compared to open surgical resection [8–10].

Thermal ablation has been used to treat tumors in organs including the liver, kidney, and lung, bone, and soft tissues, which makes it a versatile option for treatment of both iCCA and metastatic disease. The most common ablation techniques include high temperature ablation with microwave ablation (MWA) and radiofrequency ablation (RFA) and low temperature ablation with cryoablation. RFA applies a high-frequency alternating current to tumor cells to generate temperatures up to 100 C and causes local coagulative necrosis. MWA is a more recently developed hyperthermic ablative technique that induces a local electromagnetic field to oscillate water molecules within cells. The resultant kinetic energy results in heating of local tissue to greater than 100 C [11] (Fig. 18.1). MWA can produce larger ablation zones than RFA, as propagation of the RFA ablation zone is limited by current impedance caused by desiccation of tissues. In addition, MWA is less susceptible than RFA to heat-sink effect caused by adjacent vascular structures. With less thermal energy dissipation by flowing blood, probability of tumor-kill is increased with decreased risk of local recurrence [12].

Cryoablation uses extreme low temperatures to cause direct cellular injury and tissue necrosis. The freezing temperatures of cryoablation are generated based on the gas-throttling Joule-Thomson effect, with gas expansion after being forced through a valve resulting in local cooling. During cryoablation, a liquid gas (e.g., argon) flows through the cryoablation probe before rapidly expanding within a chamber at the tip of a probe to generate temperatures down to −160 C in the surrounding tissues. Lethal temperature for tumor cells is typically between −20 and −40 C, with cell death mediated by multiple mechanisms including cell membrane damage by ice crystal formation, vascular injury and thrombosis, and induction of coagulative necrosis [13]. Cryoablation is unique

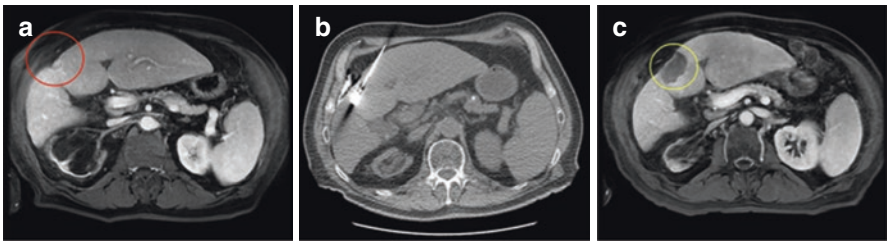

Fig. 18.1 Patient with multifocal intrahepatic cholangiocarcinoma intolerant of chemotherapy. Left hepatic lesions (not shown) were treated with left-lobar Y90 radioembolization. This single right-sided lesion shown on contrast-enhanced MRI (**a**, red circle) was amenable to microwave ablation (**b**). Note high-density hydrodissection (saline with dilute iodinated contrast) to protect peritoneum from thermal injury. One month post-ablation (**c**), contrast-enhanced MRI demonstrates ablation zone with no residual tumor (yellow circle)

among thermal ablation techniques in that it allows for real-time visualization of the cryoablation zone by CT to confirm treatment of the target region.

Novel ablation techniques including irreversible electroporation and high-intensity focused ultrasound have promising initial data regarding safety and efficacy. Irreversible electroporation delivers electrical pulses via percutaneous probes to destabilize cell membranes and induce pore formation to trigger cell death. Histologic studies have demonstrated that irreversible electroporation preserves collagen structures and extracellular matrix within the ablation zone, which makes it an attractive potential option for hepatic tumors in close proximity to vascular structures and bile ducts [14–16]. High-intensity focused ultrasound is an ablative technique that does not require percutaneous probe placement and is performed completely noninvasively. The technique focuses high-intensity ultrasound beams on a small volume of tissue to generate heat and induce coagulative necrosis [17, 18]. Further investigation is necessary to determine the utility of these techniques in the setting of iCCA.

Efficacy and Safety Data

The vast majority of studies on thermal ablation of iCCA have examined the outcomes of hyperthermic ablation with RFA and MWA. Although there is robust outcomes data for cryoablation in the setting of hepatocellular carcinoma and hepatic metastases, additional studies are needed to confirm similar efficacy in the setting of iCCA.

Several retrospective case series have examined the safety and efficacy of radiofrequency ablation in the setting of primary and recurrent CCA. The first case report of radiofrequency ablation for iCCA was published in 2002, which reported technically effective ablation of a single intrahepatic recurrence without evidence of residual disease for 10 months of follow-up [19]. Additional case series on RFA have demonstrated primary efficacy ranging between 70% and 92%, with primary efficacy defined as no evidence of residual tumor on follow-up imaging at 1 month [20–23]. A meta-analysis of radiofrequency ablation in the setting of CCA by Han et al. comprising 84 patients reported median survival time from time of procedure ranging between 20 and 60 months and pooled 1-year, 3-year, and 5-year survival of 82%, 47%, and 24%, respectively. Pooled local tumor progression at 1 month was 21% [24]. Prognostic factors for improved progression-free survival following RFA include fewer treated lesions and smaller tumor size [24, 25].

MWA has demonstrated similar efficacy in the treatment of both primary and recurrent iCCA. A retrospective study by Zhang et al. with 107 patients treated with MWA reported median progression-free survival of 8.9 months and median overall survival of 28 months [26]. An additional retrospective study by Yu et al. demonstrated primary efficacy of 87.5% and overall survival at 6, 12, and 24 months of 79%, 60%, and 60%. Local tumor progression at 4 months was observed in 10.5%

of patients with tumors less than 5 cm and 56% for tumors greater than 5 cm [27]. A study comparing outcomes of MWA and RFA to surgical resection in the setting of recurrent CCA demonstrated no significant difference in disease-free survival or overall survival between the two groups [28]. The incidence of major complications was significantly higher for surgical resection compared to percutaneous ablation (46.9% vs. 3.9%). However, in subgroup analysis of patients with tumors greater than 3 cm, there was greater overall survival in the surgical resection group compared to thermal ablation.

Combination of thermal ablation with additional adjunctive interventional radiology treatments has the potential to further improve efficacy of ablation in the setting of larger tumors. For example, a study by Peng et al. comparing combined RFA with transcatheter arterial chemoembolization (TACE) to RFA alone demonstrated significantly improved overall survival with the combined therapy for lesions greater than 5 cm and in the setting of multiple lesions. Progression-free survival for the combined RFA and TACE at 1, 2, and 3 years was 93%, 83%, and 75% [29]. An additional study by Yang et al. on combined MWA with TACE demonstrated similar improved primary efficacy of 92% without any major complications [30].

Both RFA and MWA are relatively well-tolerated procedures with low rate of complications. A meta-analysis of radiofrequency ablation for CCA reported a major complication rate of 5.9%, which included two cases of liver abscess, biliary stricture, pleural effusion requiring thoracentesis, and pseudoaneurysm formation requiring coiling embolization [24]. Similarly, Zhang et al. reported a low major complication rate of 2.8% among 107 patients that underwent microwave ablation for CCA [26]. In patients that have many medical comorbidities that are poor surgical candidates, thermal ablation is an important potentially curative treatment option to consider.

In addition, thermal ablation combined with immunomodulatory therapies (e.g., checkpoint inhibitors) is an emerging focus in oncology research [31, 32]. Studies have demonstrated that thermal ablation results in a local inflammatory response and stimulation of the immune system [33]. Augmentation of this response with immunotherapy aims to turn exposed tumor antigens into in situ vaccines to trigger a distant antitumor immune response, analogous to the abscopal effect described within the field of radiation oncology. A pilot study by Xie et al. investigated the efficacy of combined anti-CTLA-4 therapy (tremelimumab) and microwave ablation in 20 patients with unresectable biliary tract cancer [34]. Median progression-free survival and overall survival were 3.4 months and 6.0 months, respectively, with an overall response rate of 12.5%. The combined therapy demonstrated an increased global immune response, with peripheral blood flow cytometry showing an approximately threefold increase in activated CD8+ T cells in circulation following treatment. The correlation between the observed immune response and local antitumoral effects requires further investigation. Several additional ongoing clinical trials are currently studying the efficacy of combined thermal ablation with immunotherapy to assess the potential role for this combined therapy in the future of oncology care.

Chemoembolization

Overview

TACE is a minimally invasive endovascular procedure which allows for selective delivery of chemotherapy and embolic material directly to tumor cells in the liver. Originally developed in the 1970s as a treatment for hepatocellular carcinoma, TACE has developed into an important palliative treatment option for unresectable and liver-dominant metastatic iCCA [35, 36].

The liver receives a dual blood supply from both the portal veins and the hepatic arteries. However, hepatic malignancies such as CCA receive the majority of their blood supply from the hepatic arteries [37]. This characteristic allows intra-arterial therapies such as TACE to be effective even for relatively hypovascular malignancies such as CCA. The treatment effect of TACE is mediated by two main mechanisms: concentrated chemotherapy delivery to the tumor and embolic occlusion of hepatic arteries supplying the tumor [38]. Selective delivery of chemotherapy allows a concentrated dose to be administered to the tumor with decreased risk of systemic side effects. Embolization of the hepatic artery has the combined benefit of causing tumor ischemia and increasing retention of chemotherapy within the tumor.

During TACE, the chemotherapy agent is delivered intra-arterially either in combination with lipiodol, an ethiodized oil contrast agent, followed by an embolic agent (e.g., Gelfoam or polyvinyl alcohol) or coated on drug-eluting beads (Fig. 18.2). Administration of chemotherapy in combination with lipiodol and an embolic agent is referred to as conventional TACE (cTACE). The most commonly utilized chemotherapeutic agents utilized during cTACE for CCA include doxorubicin, cisplatin,

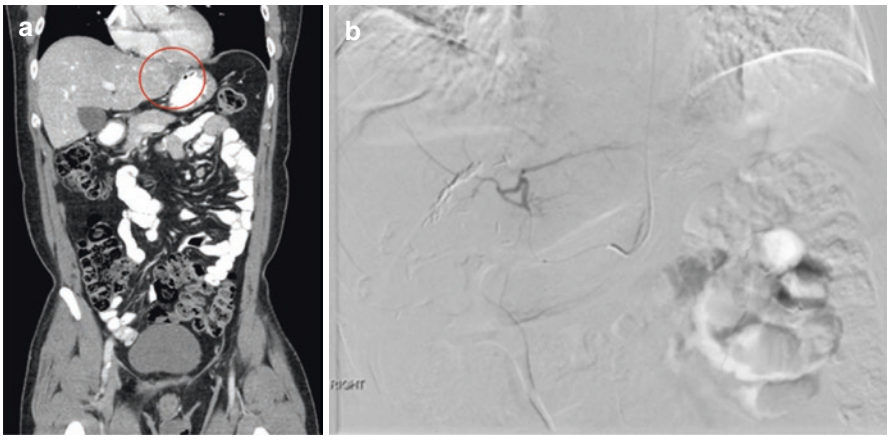

Fig. 18.2 Patient with multifocal intrahepatic cholangiocarcinoma with single lesion in segment II/III not responding to chemotherapy (**a**, red circle). Due to location near stomach and heart, doxorubicin DEB-TACE of this lesion was pursued, with left-hepatic angiogram demonstrating faint tumor blush within segment II (**b**)

gemcitabine, and mitomycin C. Administration of TACE with drug-eluting beads is referred to as DEB-TACE. DEB-TACE, which is typically performed with microbeads measuring between 100 and 300 um in diameter, allows for a sustained release of the chemotherapy from microbeads lodged within the tumor vasculature to maximize the cytotoxic effect [39, 40]. DEB-TACE for CCA is most commonly performed with beads coated with either doxorubicin or irinotecan. Bland transarterial embolization (TAE), which involves embolization of the tumor vasculature without combination with chemotherapy, is another well-recognized approach, and several studies have demonstrated no significant difference in survival benefit compared to cTACE and DEB-TACE in the setting of hepatic malignancies [41, 42].

While TACE may induce local disease control in some patients, it is typically palliative rather than curative. A study by Lee et al. demonstrated residual viable CCA post-TACE in 100% (13/13) of explants following LT. The average percentage tumor necrosis following TACE for patients with CCA was 7.6%, significantly lower than 75.1% tumor necrosis observed for patients with HCC in the same study [43]. Patients with unresectable iCCA routinely undergo multiple TACE treatments in order to control or delay progression of disease. Regular follow-up imaging after TACE is crucial to guide decision-making regarding further treatment with TACE or another therapeutic modality.

Efficacy and Safety Data

Retrospective studies on conventional TACE in the context of unresectable iCCA have demonstrated mean survival between 12 and 21 months post-treatment [35, 44–46]. A retrospective study by Park et al. compared outcomes for 72 patients that underwent cTACE and 83 patients that received supportive therapy alone and demonstrated a significant survival benefit in favor of cTACE of 12.2 months compared to 3.3 months. Another retrospective study by Kiefer et al. with 62 patients showed that cTACE further improves survival when administered sequentially after systemic chemotherapy, with median survival of 28 months with combination therapy relative to 16 months with TACE alone [44]. The treatment benefit of cTACE compared to surgical resection was assessed in a retrospective study by Scheuermann et al., which demonstrated superior median survival for R0 surgical resection compared to cTACE, but no significant difference in median survival for cTACE compared to margin positive resection [47]. Poor prognostic factors for survival in patients undergoing cTACE for iCCA include large tumor size, tumor hypovascularity, Child-Pugh class B, and early tumor progression on imaging following the procedure [45, 48].

DEB-TACE has also been shown to be of value for patients with iCCA. Retrospective studies have demonstrated median survival post-DEB-TACE to be between 12 and 13 months, similar to reported results for cTACE [49, 50]. In a study by Schiffman et al. with 24 patients, DEB-TACE demonstrated improved median overall survival when performed sequentially following systemic chemotherapy (FOLFOX or GEMZAR) compared to systemic chemotherapy alone (17.5 vs. 7.4 months) [49].

Patients that undergo TACE may develop post-embolization syndrome in up to 20–40% of cases, with common symptoms including right upper quadrant pain, nausea, fever, and serum transaminase/bilirubin elevation [51, 52]. These side effects typically self-resolve within 24–48 hours and may require an overnight hospitalization for observation. Major complications from nontarget embolization including gastrointestinal ulceration/perforation, liver abscess, or cholecystitis are rare and occur in less than 2–5% of patients [53, 54].

Most studies on TACE in the setting of iCCA are limited by their retrospective nature and the lack of standardized treatment protocols. Differences in chemotherapeutic agents, embolic agents, and operator experience limit comparison between different types of TACE procedures and other second-line therapeutic options. Based on current evidence, there is no significant difference in overall survival benefit for cTACE compared to DEB-TACE [55, 56]. Future prospective studies are required to better assess the treatment benefit of TACE and evaluate the relative efficacy of DEB-TACE versus cTACE, as well as appropriate combinations with chemotherapy regimens.

Radioembolization

Overview

TARE involves intra-arterial delivery of radioactive microspheres to liver tumors via the hepatic arteries [57]. Similar to TACE, this procedure draws on the concept that hepatic malignancies derive the majority of their blood supply from the hepatic arteries. TARE is performed with Yttrium-90 (^{90}Y)-coated microspheres, which emit high-energy beta radiation with a half-life of approximately 64.2 hours. The Y90-coated microspheres emit high-energy radiation with a mean penetration depth of approximately 2.5 mm, thereby sparing much of the surrounding tissue outside the area of deposition [58, 59]. ^{90}Y radioembolization is also sometimes referred to as selective internal radiation therapy (SIRT) (Fig. 18.3).

There are currently two types of ^{90}Y microspheres available: glass microspheres (TheraSpheres, BTG international) and resin microspheres (SIR-Spheres, Sirtex Medical). Selection of Y90 microsphere type is dependent on operator experience and preference. The two types of microspheres differ in size, with resin microspheres measuring 20–60 um compared to 20–30 um for glass microspheres, and radiation activity, with glass microspheres associated with a higher radiation dose per microsphere compared to resin microspheres. Resin microspheres are FDA approved for treatment of metastatic colorectal cancer to the liver, while glass microspheres are approved with a humanitarian device exception for patients with unresectable hepatocellular carcinoma. However, both are utilized in an investigational and off-label capacity in the context of iCCA.

Although intra-arterial administration of radioactive microspheres allows for high doses of radiation to be delivered selectively to tumors, nontarget delivery

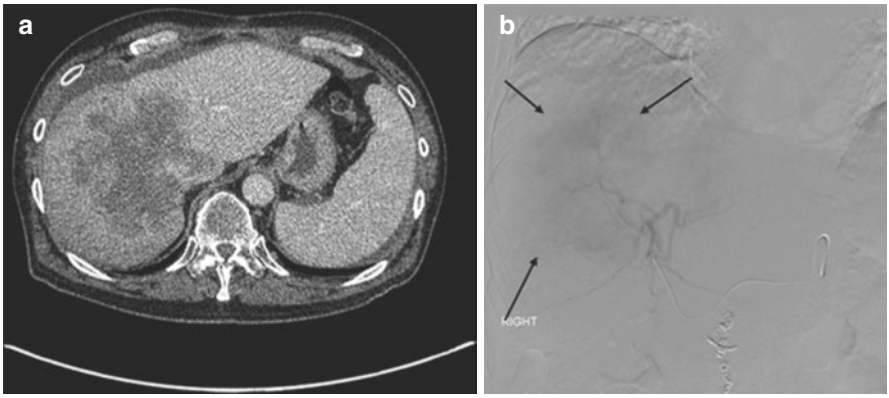

Fig. 18.3 Patient with unresectable liver confined intrahepatic cholangiocarcinoma shown as hypodense mass on axial contrast-enhanced CT (**a**). Patient underwent Y90 radioembolization (**b**). Faint tumor blush can be appreciated on this delayed right hepatic artery angiogram

of the dose has the potential to cause radiation-induced side effects. In order to reduce the risk of nontarget radioembolization, a planning procedure to localize and quantify the anticipated distribution of Y90 microspheres is performed approximately 1–2 weeks prior to the therapy [60]. ^{99m}Technicium-macroaggregated albumin (^{99m}Tc-MAA), a diagnostic radiopharmaceutical that is similar in size to Y90 microspheres, is administered intra-arterially to the hepatic arteries supplying the tumor. SPECT-CT is performed immediately afterward to assess the distribution of particles. The lung shunt fraction, which is the anticipated proportion of the radiation dose delivered to the lungs, is calculated based on the SPECT-CT results to assess the risk for radiation pneumonitis [61] (Fig. 18.4). Progressive dose reduction is typically performed as the lung shunt fraction increases above 10% of the total dose. A radiation dose to the lungs of greater than 30 Gray (Gy) in a single treatment or 50 Gy over a series of treatments is a relative contraindication to TARE [62]. Pre-procedural angiography during 99mTc-MAA administration has the added benefit of characterizing the arterial supply to the tumor and providing an opportunity to coil nontarget arteries that supply the gastrointestinal tract that may arise from hepatic arteries.

Efficacy and Safety Data

TARE has been shown to improve survival in the setting of liver-confined unresectable iCCA relative to historical controls. In several retrospective studies on Y90 TARE for unresectable and limited metastatic disease, medial overall survival from time of procedure ranged between 9.3 and 22 months [63–66]. Factors associated with increased overall survival include higher baseline performance status (ECOG

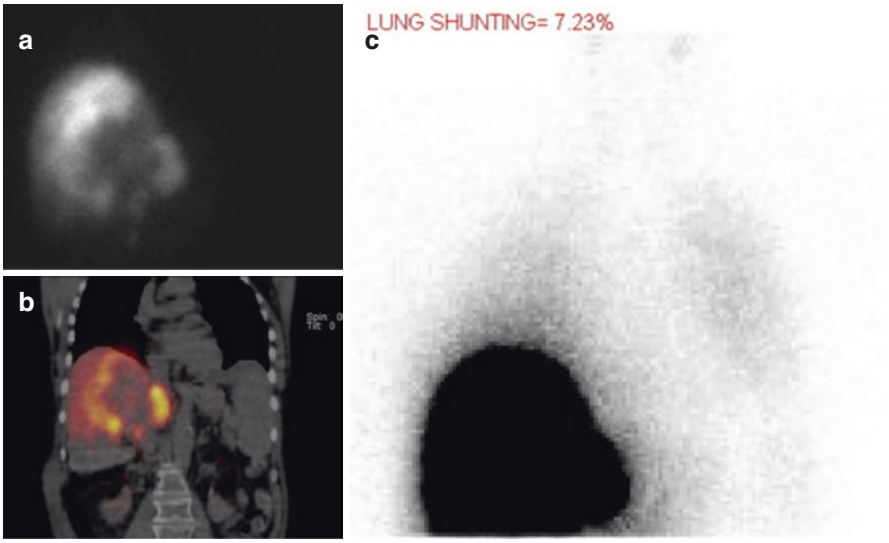

Fig. 18.4 ^{99m}Tc-labeled-MAA scintigraphy was performed in a 68-year-old man with intrahepatic cholangiocarcinoma. (**a**) Single photon emission computed tomography (SPECT) imaging performed by rotating a gamma camera around the patient, which demonstrates high uptake in the expected location of the liver. Region of photopenia in the left lobe of the liver corresponds to an area of central necrosis within a dominant mass. (**b**) SPECT radiotracer uptake superimposed on a low-dose attenuation correction CT demonstrates that the uptake corresponds to the liver without evidence of significant extrahepatic uptake. (**c**) Hepatopulmonary shunt fraction calculated based on planar scintigram demonstrates a lung shunt fraction of 7.23%. The patient was able to undergo successful treatment without radiation dose reduction

0 or 1), tumor burden involving <25% of the liver volume, tumor response to treatment (i.e., partial response or stable disease), and higher radiation dose delivered [64, 66]. Decreased overall survival was associated with increased INR, bilirubin, CA 19–9, ALT, and MELD score post-treatment [67]. A prospective multicenter observational study on the safety and efficacy of TARE for unresectable or limited metastatic, chemotherapy refractory iCCA by White et al. demonstrated overall survival of 8.7 months and progression-free survival of 2.8 months at a median follow-up of 13.9 months [68]. Overall, survival outcomes for TARE are comparable to alternative intra-arterial therapies including cTACE and DEB-TACE. However, there are no randomized clinical trials directly comparing efficacy of TARE, TACE, and other second-line therapies for iCCA. A meta-analysis by Boehm et al. comparing outcomes from TARE and TACE demonstrated slightly higher median overall survival for TARE compared to TACE (13.9 +/− 4.4 months vs. 12.4 +/− 1.5 months). The response to therapy demonstrated in the meta-analysis (complete or partial response) was higher for TARE compared to TACE (27.4 +/− 10% vs. 17.3 +/− 11.5%) [56].

Treatment with TARE also has the potential benefit of downstaging patients with borderline unresectable tumors into surgical candidates. In a study by Mouli et al.,

46 patients with unresectable iCCA were treated with a total of 92 total TARE treatments. Among the 46 patients, 5 (11%) had disease response that allowed them to be converted to resectable status and undergo curative R0 resection [69]. Another phase II clinical trial combining first-line chemotherapy and TARE for unresectable disease demonstrated an overall response rate of 39% by RECIST criteria and allowed 22% of patients to be downstaged to surgically resectable status [70]. The survival benefit of downstaging tumors for surgical resection was demonstrated in a retrospective study by Bourien et al., in which 19% of the patients were downstaged to surgical resection and had a subsequent median overall survival of 51.9 months, which was significantly higher than 16.4 months for patients treated with TARE alone [64].

TARE is well tolerated in the majority of patients and is typically performed as an outpatient procedure. Following the procedure, patients may develop post-radioembolization syndrome in up to 20–40% of cases, which includes fatigue, nausea, malaise, and right upper quadrant pain. The symptoms of post-radioembolization syndrome are typically less severe than post-embolization syndrome observed following TACE and rarely require hospitalization. Side effects related to nontarget deposition of radioactive microspheres including gastrointestinal ulceration, radiation pneumonitis, and liver dysfunction are relatively rare [71, 72].

Conclusion

Most patients with iCCA are diagnosed at an advanced stage and have a poor prognosis. Although surgical resection and LT are potentially curative treatment options, only a minority of patients have resectable disease at the time of diagnosis. In patients with unresectable and liver-confined or liver-dominant metastatic disease, locoregional therapies performed by interventional radiology offer effective palliative options. Thermal ablation and arterially directed therapies such as TACE and TARE have demonstrated survival benefit in retrospective studies comparable or even favorable to standard-of-care systemic chemotherapy. In addition, interventional radiology procedures are minimally invasive with lower risk for complications compared to surgical resection.

Robust clinical data on the efficacy of interventional radiology procedures for iCCA is limited by the rarity of the disease, lack of standardized treatment protocols, and retrospective nature of the majority of published studies. In addition, the technology within the field of interventional radiology evolves rapidly, with new devices and equipment being utilized every few years. Updated prospective trials will be necessary to accurately assess the efficacy of interventional radiology procedures and develop evidence-based indications and guidelines.

Overall, interventional radiology treatments such as thermal ablation and arterially directed therapies should be considered important components of the treatment arsenal for unresectable iCCA. In the setting of liver-confined or liver-dominant disease, these therapies can be used in combination with or as an alternative to systemic chemotherapy.

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