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INTERVENTIONAL ONCOLOGY (DC MADOFF, SECTION EDITOR)

Locoregional Therapy in the Management of Intrahepatic Cholangiocarcinoma: Is There Sufficient Evidence to Guide Current Clinical Practice?

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Abstract

Purpose of Review Intrahepatic cholangiocarcinoma (iCCA) carries a dismal prognosis and, despite increasing incidence, still lacks effective treatments. In this scenario, locoregional therapies (LRT) are gaining interest as they may be effective at local tumor control and complementary to surgical and non-surgical approaches. In this article, we will review the evolving role of LRT performed by interventional radiologists in the management of iCCA.

Recent Findings Accumulating retrospective evidence indicates that ablative therapies and transarterial embolizations are of benefit for iCCA with unresectable disease, demonstrating promising safety profiles and prolonged or comparable survival outcomes compared to systemic therapy and surgery. Additionally, for surgical candidates, portal ± hepatic venous embolization can improve the safety of hepatectomy by inducing preoperative hypertrophy of the non-involved liver lobe.

Summary LRTs are playing an increasingly important role in the multimodal treatment of iCCA from various perspectives with reduced toxicity relative to traditional treatments. To expand the scope of applications for LRTs in this setting, future prospective randomized studies are needed to confirm their efficacy and advantage.

Introduction

Cancers of the biliary tract arise from the epithelial cells of the biliary system and are classified based on the anatomical locations, including extrahepatic cholangiocarcinoma, intrahepatic cholangiocarcinoma (iCCA), and gallbladder cancer [1]. Relative to hepatocellular carcinoma, less epidemiology is known regarding iCCA. The prevalence and incidence of iCCA are frequently grouped together with hepatocellular carcinoma as a single category of primary liver cancer. It is predicted that there will be around 30,000 deaths related to primary liver cancer in 2022. As the second most common primary intrahepatic malignancy, iCCA accounts for approximately 20% of the deaths with a 5-year survival rate less than 20% [2–4]. Previous studies have demonstrated increased global incidence of intrahepatic cholangiocarcinoma but stable or decreased incidence of extrahepatic cholangiocarcinoma [5]. Surgical resection remains the only potentially curative treatment option for iCCA; however, more than 70% of the patients are not surgical candidates at the time of presentation due to their anatomical location, the presence of metastasis or the inadequate functional reserve of the potential future liver remnant (FLR) [6]. Of all the patients who undergo surgery, only one-third lives more than 5 years despite having negative postsurgical margins [7]. Administration of first-line systemic therapies (e.g., gemcitabine and cisplatin) offered unsatisfactory survival benefits with a median survival time of 11.2 months among patients with advanced biliary tract cancer [8, 9]. Targeted medical therapy is still in its early stages of development but has demonstrated promising potentials. In a phase 3 clinical trial, *IDH1* variant-targeted inhibition with ivosidenib demonstrated improvement in survival outcome compared to placebo in patients with unresectable or metastatic cholangiocarcinoma [10]. A recent phase 3 clinical trial from South

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Korea showed that PD-L1 inhibition in combination with chemotherapy conferred a 1.5-month survival advantage compared to chemotherapy alone [11]. However, at present, there is no clear winner in terms of a medical alternative for iCCA [12, 13••]. Resistance to therapy and a lack of developments in targeted therapeutic strategies for iCCA can be partially attributed to cellular and histological heterogeneity, and its desmoplastic and infiltrative nature. Such features are responsible for immune evasion, invasive growth, and metastasis, and thus associated with poorer survival outcomes [14].

The limited therapeutic efficacy of current treatment options, anatomic considerations offered by variable iCCA phenotype, and end organ intolerance to surgical resection or radiotherapy makes image-guided percutaneous interventions an aspirational approach with emerging reports that support their usefulness. For patients who are surgical candidates, percutaneous interventions such as portal vein embolization are effective at inducing liver hypertrophy of the anticipated FLR prior to definitive therapy [15]. For patients who are non-surgical candidates, various LRT modalities have demonstrated oncological benefits in both treatment naïve and recurrence groups [16]. This literature review aims to discuss current algorithms in the management of iCCA, the roles of LRT in the management of iCCA, and explore its future potential in the multimodal management of iCCA.

Overview of Current Algorithms and Guidelines for Management of iCCA

As cancer care transitions to a personalized multimodal approach, optimized care requires a high quality, evidence-based staging system which allows for reliable prediction of prognosis, development of treatment plan, and objective comparison of efficacy and outcomes among studies. One such example is the Barcelona Clinic Liver Cancer (BCLC) staging system for hepatocellular carcinoma (HCC), which links the stage of disease to treatment strategy and was validated by both retrospective and prospective analyses [17]. It is endorsed by the European Association for the Study of the Liver (EASL) and the American Association for the Study of Liver Diseases (AASLD), providing the best prognostic and treatment stratification for HCC patients among over 15 existing HCC staging systems [17, 18]. In comparison, the development of an iCCA treatment algorithm remains at a far earlier stage, which is largely attributed to the historical low incidence of iCCA. Several staging systems have been proposed for the treatment of iCCA including two Japanese staging systems, one by Yamasaki et al. and one by Okabayashi et al., but they failed to demonstrate consistent performance in prognostic prediction in subsequent validating studies [19–21]. Until the 7th edition of The American Joint Committee on Cancer (AJCC) cancer staging manual, iCCA was grouped with HCC under primary hepatic malignancy. By far, the AJCC 7th edition, and now, the AJCC 8th edition staging systems are the most internationally recognized staging guideline for iCCA and have been externally validated with better prognosis predictability [18, 22, 23]. The consensus among guidelines for patients with earlier stage iCCA is to achieve a negative margin with surgical resection [23]. For patients with advanced and metastatic disease, the first-line management is less clear. The algorithm proposed by the EASL based on the AJCC 7th edition (Fig. 1), as well as the most recent 2021 NCCN (National Comprehensive Cancer Network) guideline support the role of locoregional therapy as a potential initial treatment in patients with non-metastatic, but unresectable disease; other potential choices include systemic therapy, immune therapy, or radiation [13••, 18]. Further implementation of an effective treatment algorithm requires more research on understanding the pathogenesis of iCCA that distinguishes it from other primary hepatic malignancies, as well as adequately powered randomized controlled trials to justify the choice of treatments.

Optimizing the Anticipated Future Liver Remnant Before Surgery

For the few patients who are diagnosed with iCCA at an early stage, surgery holds the strongest evidence as a curative intent treatment. However, patients who undergo hepatic resection for the treatment of iCCA are at risk for developing postoperative complications, such as post-hepatectomy liver failure (PHLF), bile leak, and gastrointestinal tract bleeding [24]. The volume and function of FLR are strong indicators for the risk of PHLF, which is associated with a high mortality rate [15, 25]. For patients at risk of developing PHLF, hypertrophy of the FLR is indicated prior to hepatic resection. Available methods that promote hypertrophy of the FLR include portal vein embolization (PVE), liver venous deprivation (LVD), and associating liver partition and portal vein ligation for staged hepatectomy (ALPPS). Among these approaches, PVE and LVD are performed percutaneously by interventional radiologists. The ratio of FLR/total estimated functioning liver volume (TELV) designated as standard FLR (sFLR) and liver function assessment by hepatobiliary scintigraphy are used as parameters to track progress of hypertrophy and predict the likelihood of PHLF [15, 25–27]. PVE is an effective approach to induce hypertrophy of the FLR by redirecting blood flow from the tumor-bearing liver towards the anticipated FLR. It is established as the standard of care for preoperative liver hypertrophy worldwide [28]. Typically at our center, PVE is performed with 100–300-μm particles followed by coil embolization of proximal vessels

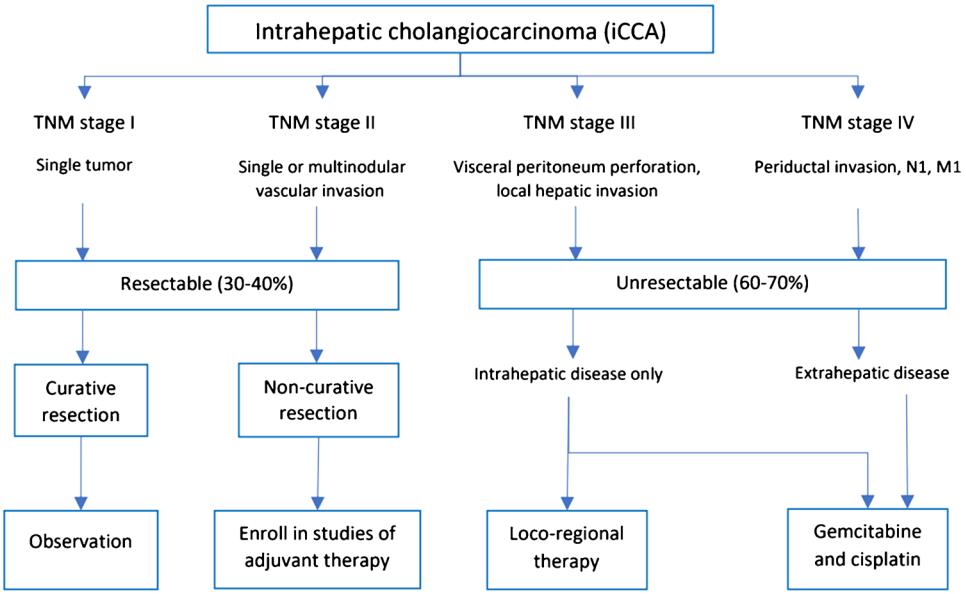

Fig. 1 Adapted from Journal of Hepatology, 2014, by Bridgewater et al. EASL recommendation of iCCA treatment algorithm based on AJCC 7th edition staging system [18]

[29, 30]. The resultant hypertrophied left lobe is as shown in Fig. 2. One drawback of PVE is that the time required for adequate FLR hypertrophy is usually 4–5 weeks, during which tumor progression may prohibit a safe hepatectomy in up to 20% of the patients [25]. Compared to PVE, LVD involves the embolization of the ipsilateral right with or without the middle hepatic vein in addition to the portal vein. Studies have shown that LVD may achieve faster FLR growth compared to PVE without affecting mortality [25, 31, 32]. A retrospective analysis by Guiu et al. comparing PVE and LVD including 51 patients undergoing major hepatectomy demonstrated improved FLR function (+63.9% vs. +29.8%, $p<0.001$) and increased FLR volume (+52.6% vs. +18.6%, $p=0.001$) at day 21 in the LVD group [25]. In a retrospective study conducted by Kobayashi et al., significantly increased volume of FLR and higher median kinetic

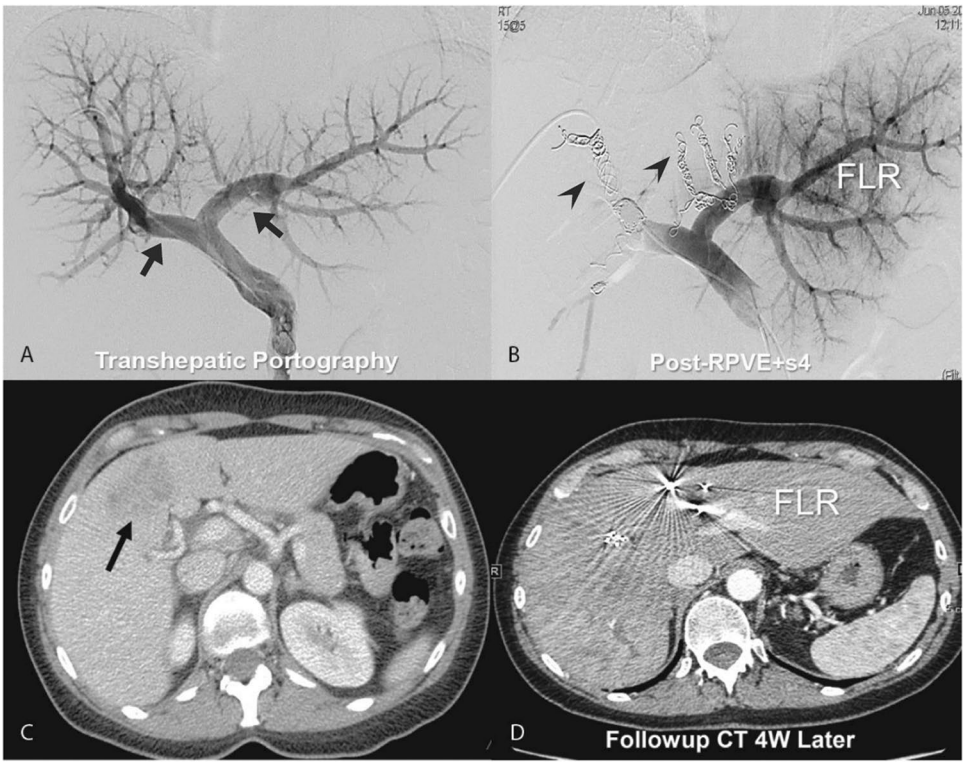

Fig. 2 **A**, **B** Transhepatic portography before and after embolization. Arrows: contrast opacified left and right portal veins. Arrowheads: coil embolization of the right portal vein with extension to segment IV branches. **C** Pre-PVE, right hepatic lobe iCCA (arrow); **D** hypertrophied FLR 4 weeks after PVE

growth rate were observed in the group treated with LVD compared to PVE [32]. The adverse effects of PVE are rare and usually do not affect FLR hypertrophy, which include subcapsular hematoma, migration of coil, or embolizing material [28]. Compared to PVE, no significant difference in complications after LVD was observed. The theoretical liver necrosis due to simultaneous hepatic and portal vein embolization was not seen in prior published results [33]. Contrary to prior reports, a prospective matched cohort study of 20 patients by Böning et al. reported that LVD did not show significant advantage in liver hypertrophy compared to PVE [34]. The discrepancy can be attributed to the differences between retrospective and prospective nature of the studies, sample size, and embolization sequence and technique.

Compared to PVE and LVD, the surgical approach ALPPS can induce a fast hypertrophy rate (+49% at 8 days); however, an early international ALPPS registry reported unacceptable morbidity and mortality rates: 28% patients experienced severe complications, NCI/WHO grade ≥ 3b, with a 9% 90-day mortality rate [32]. Thus, the authors concluded that PVE and LVD are effective options for iCCA patients with resectable tumors but small sFLRs [32]. Based on retrospective studies, LVD has the potential to provide more benefits in terms of increased rate of FLR hypertrophy and improved FLR function. However, prospective randomized trial data will be needed to confirm this hypothesis. Phase II trials including HYPER-LIV01 and DRAGON-2 comparing the efficacy of LVD vs. PVE in FLR hypertrophy are ongoing [35••, 36]. It is worth mentioning that these two prospective randomized trials excluded patients with primary hepatic malignancies or patients with underlying liver disease, and no dedicated studies were conducted in patients with iCCA only. Thus, the effects of hypoxia induced by PVE or LVD on tumor progression in iCCA, which particularly thrives in hypoxic environment, is unknown [37]. Further studies in this area dedicated to this population are necessary to draw effective conclusions.

Local Ablative Therapies

Thermal ablative therapies such as radiofrequency ablation (RFA) or microwave ablation (MWA) aim at total tumor destruction for optimal local control. They are most applied for patients who are not surgical candidates with small tumor size (ideally less than 3 cm but can be up to 5 cm) or patients who have developed recurrence after surgical resection. Smaller and fewer tumors that are away from the hepatic hilum or adjacent organs are preferred to avoid heat-induced damage. Proximity to major blood vessels can also cause incomplete ablation due to heat sink effect [38, 39]. Previously published meta-analysis and systematic review of seven observational studies encompassing 84 patients demonstrated that percutaneous RFA is an effective treatment that prolongs survival for patients with inoperable iCCA. The pooled 3- and 5-year overall survival (OS) rates were 47% and 24%, respectively [40]. According to two separate single-center retrospective studies, tumor diameter ≥ 2 cm and hepatic recurrence within 1 year after resection were associated with poor survival outcomes [41, 42]. Incomplete ablation is associated with tumors ≥ 5 cm, despite initial downstaging with transarterial chemoembolization (TACE) [43, 44]. Due to the desmoplastic nature of iCCA, a wider ablation zone is required to eradicate invisible tumor, which poses as a potential technical challenge even for relatively smaller tumors [38]. Adverse events associated with RFA are rare, though include pleural effusions, biloma, and liver abscess, which are usually adequately managed by drainage [42, 43, 45]. When comparing clinical outcomes in patients with recurrent iCCA who received RFA vs. hepatic re-resection, Zhang et al. demonstrated that adverse events were significantly lower in patients who were treated with RFA compared to surgical re-resection with no difference in median OS [46].

Compared to RFA, there are fewer studies of MWA in the treatment of iCCA. One of the largest retrospective analyses studied the safety and efficacy of MWA in 107 non-surgical candidates with iCCA ≤ 5 cm. Patients who underwent MWA demonstrated favorable outcome compared to palliative treatment alone or radical surgical resection. The overall survival rates at 3 and 5 years were 39.6% and 7.9%, respectively [47•]. Xu et al. compared the efficacy of MWA ($n = 56$) to surgery ($n = 65$) in 121 patients with recurrent iCCA. The median 5-year OS for MWA and surgery was 23.7% and 21.8%, respectively, without statistically significant difference. Major complication rates were higher in the surgical group (13.8% vs. 5.3%, $p = 0.007$) [48]. Adverse effects associated with MWA are overall well tolerated and similar to RFA. In MWA, tumor number, Child–Pugh class, ALBI grade, and metastasis were identified as prognostic factors [47•, 48]. A recently published randomized controlled phase II trial comparing the efficacy of MWA vs. RFA in the treatment of primary hepatic malignancy (between 1.5 and 4 cm) demonstrated no significant difference in complication rates, overall survival, or median time to progression, suggesting that both modalities are suitable treatment options [49].

Data supporting the efficacy of cryoablation in the treatment of iCCA is scarce. Cryoablation induces coagulative necrosis of tumor through freeze–thaw cycles. Although all ablative modalities have been documented to trigger a post-ablative immune response against cancer compared to surgery, cryoablation is especially known to preserve intracellular tumor antigen including DNA, RNA, and heat shock proteins during the ablative process, thus eliciting more potent systemic anti-tumor immunity, evidenced by increased serum interleukin-1, interleukin-6, and others

[50]. Since cryoablation in the liver can cause higher incidence of hemorrhage, and a rare but unique complication called "cryoshock," characterized by multiorgan failure and severe coagulopathy, cryoablation is used less frequently in the treatment of hepatic malignancies compared to other thermal ablation modalities [51].

Irreversible electroporation (IRE) is a non-thermal ablative therapy that induces apoptotic cell death using electrical impulses without involving extracellular matrix. A significant advantage of IRE is that it is not affected by heat sink effects and is safe and effective in the treatment of tumors that are adjacent to major biliary or vascular structures. Therefore, studies for IRE are mostly done in surgically unresectable perihilar cholangiocarcinoma [52–54].

Transarterial Therapies

For patients with non-resectable or metastatic disease, systemic therapies with cisplatin and gemcitabine have shown efficacy and survival benefits [9]. For the last two decades, transarterial chemoembolization (TACE) and transarterial radioembolization (TARE) have been playing an increasingly important role in patients with liver cancer, particularly in patients with large tumors (≥ 5 cm), or with recurrent disease. The goal is to prolong survival or to downstage for more definitive treatments.

TACE involves mixing an embolic agent with cytotoxic agents infused directly through a hepatic artery branch. The process prolongs exposure to cytotoxic agents while inducing ischemic cell deaths [55]. Multiple international guidelines have recommended TACE for the treatment of the intermediate stage HCC based on results from earlier randomized controlled trials [56, 57]. Thus, the application of TACE in non-resectable iCCA is promising. Retrospective analyses have demonstrated the safety and the promising efficacy of TACE in the treatment of iCCA [58–61]. Compared to systemic therapy, TACE confers a 2–7-month survival benefit in a meta-analysis of 16 studies including 542 patients [62•]. When comparing TACE alone to surgery alone, the survival outcome of patients who received TACE were lower, but similar to that of patients that underwent surgery but resulted with positive lymph nodes or positive surgical margins [63]. When used in the adjuvant setting post-curative resection, TACE did not improve recurrence-free survival, and heterogeneous results were reported in terms of the effects on OS [64–66]. In a retrospective analysis conducted on 125 iCCA patients who underwent curative resection, Shen et al. found that the group treated with adjuvant TACE demonstrated improved 5-year OS (28.3% vs. 20.8%, $p = 0.045$) [65]. Li et al. demonstrated that adjuvant TACE improved OS only in patients with TNM stages II, III, and IV, but was associated with increased postoperative recurrence in patients with TNM stage I disease [66]. Additionally, a meta-analysis study including 9 retrospective analyses with a total of 1724 patients demonstrated only short-term (1 year) survival benefits in patients who received TACE after surgery without long-term survival benefits [67]. However, it is important to note that these studies are highly heterogeneous in terms of baseline clinical characteristics and tumor features (treatment naïve vs. recurrence, tumor size, mixed hepatocellular/cholangiocarcinoma, etc.), the type of embolic agents used (e.g., lipiodol, drug-eluting beads, microspheres), the type of cytotoxic agents used (e.g., mitomycin, doxorubicin, fluorouracil, carboplatin, gemcitabine), and definition for overall survival used for measuring treatment response. Therefore, it is difficult to conduct side-by-side comparisons regarding the efficacy and outcome of each embolic method across the studies. Reported toxicities after TACE are generally less than grade 3 on NCI/WHO grading scale [62•]. Common toxicities include post-embolic syndrome (nausea, fever, abdominal pain), diarrhea, anemia, thrombocytopenia, and neutropenia [60, 68].

TARE is a type of internal radiation treatment, in which a radioactive isotope, typically yttrium-90, sealed in very small particles is delivered intra-arterially [55]. Like TACE, the patient selection for TARE in the treatment of iCCA is mainly based on clinicopathological factors due to a lack of prospective data. TARE is usually applied in patients with unresectable or recurrent disease, however more suitable for patients with increased tumor burden or diffuse tumor infiltration compared to TACE [69]. As shown in Fig. 3, a typical patient from our center with unresectable iCCA receives TARE for the treatment of a large right hepatic lobe lesion, with 3-month follow-up imaging demonstrating complete tumor necrosis. Several retrospective studies have demonstrated the efficacy and survival benefits of TARE. The reported median overall survival since TARE was between 8.7 to 14.5 months [69–73]. Studies have identified tumor burden, baseline cholinesterase level, and history of prior therapies (surgery, systemic chemotherapies, etc.) as prognostic factors [69, 71, 73–75]. The heterogeneous baseline clinical characteristics and patient selection likely contributed to the differences in the median OS in these studies.

TARE and TACE have shown negligible differences in survival outcomes in the treatment of unresectable iCCA [76, 77]. For example, in a meta-analysis, Mosconi et al. reported a median survival of 14.2 months after TACE and 13.5 months after TARE without statistically significant difference [77]. A post hoc analysis suggested that at least a 1000 sample size may be required to demonstrate the survival equivalence between TACE and TARE in the treatment of primary hepatic malignancy [78]. A benefit of TARE vs. TACE for a hypovascular tumor such as iCCA is that TARE is not dependent on vascular delivery of adequate chemoembolic agents to achieve tumor necrosis [73]. Toxicities are generally

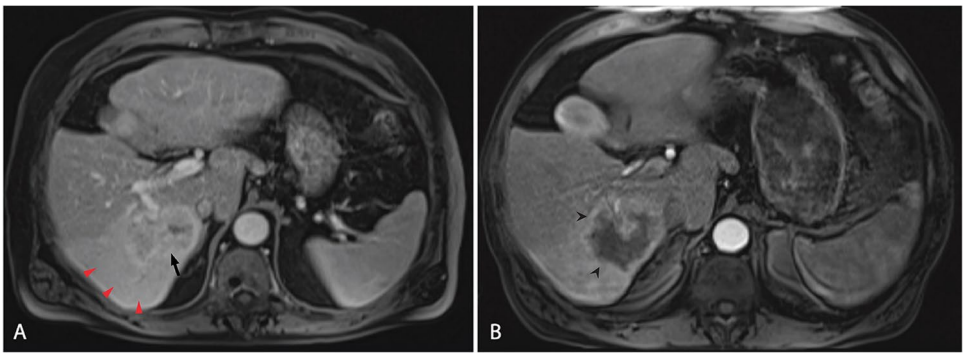

Fig. 3 **A** Pre-treatment with radioembolization demonstrating arterially enhancing right hepatic lobe mass (arrow) with areas of perfusional abnormalities (red arrowheads), confirmed as iCCA. **B** Radioembolization treated area demonstrates necrosis (black arrowheads)

well tolerated with post-embolization syndrome (nausea, fatigue, and abdominal pain) being the most common [79, 80••]. Side effects that are ≥ NCI/WHO grade 3 such as radiation-induced gastric ulceration or cholecystitis were reported but rare (1–4%), highlighting the importance of careful pre-procedural planning and patient selection to reduce the rates of complication [79, 80••]. While TARE is generally applied as a salvage therapy, a multimodal approach may be considered in an earlier stage as first-line therapy. A recently published phase 2 clinical trial evaluated the safety and efficacy of TARE plus chemotherapy (cisplatin and gemcitabine) as first-line treatment for locally advanced iCCA: the median overall survival was 22 months with 22% patient downstaged for definitive surgery [81]. Unsurprisingly, compared to previously reported complications in patients who received TARE alone, the patients that received the combined therapy experienced increased rates of adverse events (71% with NCI/WHO grade 3 or 4 toxicities) with a toxicity profile similar to systemic therapy alone [81]. The only randomized controlled trial comparing TACE and TARE in the treatment of iCCA was conducted by Kloeckner et al. including a total of 24 patients, which reflects the paucity of level I evidence supporting the choice of either treatment modality for patients with various clinicopathological characteristics [82]. The choice of modality remains largely dependent on operator preference, experience, and patient preference. For patients with marginal hepatic reserve due to underlying liver disease, TACE may be preferred due to the ability to superselect blood vessel to avoid greater radiation-induced loss of hepatic function [83]. On the other hand, TARE has the advantage to deliver adequate tumor necrosis without depending on sufficient arterial supply at the tumor bed and can be more safely administered in patients with portal venous invasion compared to TACE [84, 85]. Prospective randomized controlled trials are therefore warranted to compare the differences in efficacy and outcomes between TACE and TARE in the treatment of iCCA and better suit individual patient's clinical needs.

Future Directions

Current guidelines support surgery as the treatment of choice if the tumor is resectable. For patients who are surgical candidates, portal venous embolization is the standard of care for preoperative liver hypertrophy in patients with inadequate FLR. Several retrospective studies have demonstrated the promising potential of LVD in markedly increasing FLR volume and function, and the HYPER-LIV01 randomized clinical trial comparing the safety and efficacy of LVD and PVE is ongoing. In addition to studying the effects on FLR hypertrophy and function and short-term safety, future studies should investigate the effects of LVD or PVE on tumor progression and metastasis. For patients who are not surgical candidates, no first-line locoregional therapies have been established among international guidelines. Multiple retrospective studies have supported the evolving role of locoregional interventions in oncological treatment and preoperative downstaging. For TACE, many different forms of cytotoxic agents, embolic agents, and treatment frequency have been applied with no global guidelines, warranting further research on pharmacological mechanisms and histopathology of iCCA. There are no prospective randomized controlled studies evaluating the efficacy of TACE vs. TARE in patients with iCCA only. Given the ambiguous overlap of tumor size (≥ 3 cm) in patients who are treated with ablation vs. TACE/TARE as demonstrated by prior studies, future studies should include comparison of the efficacy of ablation vs. transarterial therapies in this patient group. As mentioned earlier, all available studies of locoregional therapies in the management of iCCA included patients with heterogeneous clinicopathological

backgrounds and used non-uniform parameters to track treatment progress (e.g., varying definitions of overall survival). Thus, it is difficult to effectively compare even with pooled analyses to increase power. The data heterogeneity may partially be attributed to the lack of universally recognized iCCA staging system with incorporation of patient's functional status, liver function, and treatment recommendations, such as the Barcelona Clinic Liver Cancer (BCLC) staging system for hepatocellular carcinoma; hence, the lack of a standard data reporting system hinders the establishment of treatment guidelines. This certainly reflects the natural process of ongoing investigation about iCCA. To answer these questions, future randomized controlled trials are needed to validify the treatment benefits and properly stratify patients for each locoregional treatment modality based on clinical background and characteristics.

Conclusion

In the era of personalized care for cancer, locoregional therapies offer a breadth of interventions that complement existing treatment and may prolong survival. Multiple retrospective studies have provided evidence in favor of the safety and efficacy of IR-directed interventions for non-resectable iCCA, while demonstrating a generally well-tolerated toxicity profile. While PVE has demonstrated its efficacy in preoperative liver hypertrophy to avoid perioperative hepatic complications, LVD is showing promising potential in accelerated liver hypertrophy and function with emerging evidence. In terms of oncological benefit, ablative and transarterial therapies have shown some, albeit limited, survival benefits in patients with surgically unresectable tumors or recurrent tumors. To broaden the scope of applications, further randomized trials are needed to confirm the beneficial impacts of IR treatments on patient survival and determine the optimal sequence of IR-directed treatments with a clear definition of indications and possibly include early-stage cases for IR treatments, in which surgery may be too risky or unfeasible. Future studies expediting patient centric investigations along with the more traditional modalities would be of tremendous value.

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Declarations

Conflict of Interest David C. Madoff, MD: Dr. Madoff reports personal fees from Boston Scientific, personal fees from Guerbet, personal fees from Johnson & Johnson, personal fees from Sirtex, outside the submitted work. All other authors declare no competing interests.

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• Of importance
•• Of major importance

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