Ablation of Intrahepatic Cholangiocarcinoma

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Abstract

Intrahepatic cholangiocarcinoma is the second most common primary liver cancer but represents only a small portion of all primary liver cancers. At the time of diagnosis, patients are often not surgical candidates due to tumor burden of other comorbidities. In addition, there is a very high rate of tumor recurrence after resection. Local regional therapies, specifically ablative therapies of radiofrequency ablation, microwave ablation, cryoablation, and irreversible electroporation, have proven to be beneficial with other hepatic tumors. The purpose of this review is to provide an overview and update of the medical literature demonstrating ablative therapy as a treatment option for intrahepatic cholangiocarcinoma.

Keywords

- intrahepatic cholangiocarcinoma
- microwave ablation
- radiofrequency ablation
- cryoablation

Cholangiocarcinoma originates from malignant transformation of biliary epithelial cells.[1] It is the second most common primary hepatic malignancy and its incidence is more than doubled during the last few decades.[2] Anatomic location dictates the classification as intrahepatic, perihilar, and distal.[1] Intrahepatic cholangiocarcinoma (IHC) represents less than 10% of all cholangiocarcinoma cases.[3] IHC can be further characterized by its morphological growth patterns into mass-forming, periductal-infiltrative, intraductal, and superficial spreading subtypes.[4] IHC has a poor prognosis and those who receive palliative treatment alone have a median overall survival (OS) of 3 months[5] and less than 10% of all patients survive more than 5 years regardless of treatment.[6] The therapeutic resistance of IHC results from its profound genetic heterogeneity, its highly desmoplastic nature, and complex tumor microenvironment in the liver.[1]

Currently, the only curative therapy is surgical resection with histologically negative margins or liver transplantation for early-stage disease. However, only a small number of patients are surgical candidates.[7] It was reported that only 6.3% of patients with IHC had surgical resection and young age was a strong predictor for receiving curative resection, while advanced age (>65) was a negative risk factor for cure.[8,9] In addition, the postresection recurrence rate is high; a recent analysis of an international surgical database of 563 patients with IHC who underwent curative-intent surgical resection demonstrated 71% recurrence rate, and 85.5% of the recurrence involved the liver and 14.5% of patients had extrahepatic-only recurrence.[10] Chemotherapy and radiation are utilized in an adjuvant or palliative settings, but their efficacy is low.[1] There is growing evidence that locoregional therapies may have an expanding role for the treatment of unresectable and recurrent IHC.[11] Meta-analysis by Han et al reported that tumor ablation increased survival in nonoperative IHC patients.[12] Due to the current technical capabilities, one of the major limiting factors of percutaneous ablative therapies is tumor size. Compounding this limitation is the infiltrative growth pattern of IHC which requires ablation zone with wide margin around the tumor.[13]

This article will review the current literature regarding the effectiveness of percutaneous ablative therapies including radiofrequency ablation (RFA), microwave ablation (MWA), cryoablation, and irreversible electroporation (IRE) in the treatment of IHC.

Radiofrequency Ablation of Intrahepatic Cholangiocarcinoma

Radiofrequency ablation is the most studied energy-based ablative method which utilizes high frequency alternating electric current that causes cell death by heating tissue through rapid electron vibration generating frictional heat.[14] This mechanism of heat generation makes RFA heavily dependent on the conductivity of the tissue which is largely correlated to

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the tissue's water content.[14,15] As the tissue adjacent to the electrode heats up, it becomes desiccated and then acts as an "insulating sleeve" hindering further generation of heat, thus limiting the ablation zone size.[14] Another factor that limits ablation zone is the cooling effect of flowing blood which works as a "heat sink."[16] Ablation zone size can be augmented by the use of multiple RFA probes.[17]

Several studies have demonstrated the successful use of RFA to treat primary IHC, and local recurrence or intrahepatic IHC metastasis after curative resection.[13,17–23] The number of patients in these reports is consistently small ranging from 6 to 20 patients.[13,17–23] These small numbers are likely attributable to the advanced stage at which most IHC is diagnosed and therefore most patients are not suitable for percutaneous ablation.[17] The most current study reported the treatment of 20 patients with a total of 50 tumors.[23] In this study, 44 tumors were treated with RFA and 6 with MWA. The median OS was 23.6 months. There was no significant difference in local tumor progression between MWA and RFA. A study of seven patients with nine IHCs, ranging in size from 1.3 to 3.3 cm (mean size of 2.4 cm), had a mean OS of 38.5 months and a 1-, 3-, and 5-year OS of 100, 60, and 20%, respectively.[18] The authors disclosed that they intentionally induced a larger ablation zone when treating IHC than they would have if they had been ablating hepatocellular carcinoma to overcome the infiltrative nature of IHC.[18] Fu et al reported median OS of 33 months with the 1-, 3-, and 5-year survival of 84.6, 43.3, and 28.9%, respectively, in 17 patients with primary IHC.[13] They attribute their outcomes to creating an ablation margin greater than 1 cm and the predominance of early-stage disease with a median tumor size of 4.4 cm $\pm$ 1.7 cm.[13] Kim et al demonstrated a median OS of 27.4 months and a mean local tumor progression-free survival of 39.8 months in 20 patients who underwent RFA of 29 recurrent IHC following surgical resection.[22] A meta-analysis of seven RFA studies of unresectable primary and recurrent IHC reported median OS range of 20 to 60 months and a combined 1-, 3-, and 5-year survival of 82, 47, and 24%, respectively.[12] This meta-analysis also recognized that treatment success was in part dependent on tumor size. Three of the studies which were included in the meta-analysis reported residual tumor after ablation when the tumor was large (>4.6 cm).[12] It also reported that there is a lower major complication rate, lower cost, and shorter length of hospital stay for RFA when compared with surgery.[12]

Microwave Ablation of Intrahepatic Cholangiocarcinoma

Microwave ablation has emerged as an alternative method to RFA that appears to overcome many limitations of RFA. Microwave technology deposits energy into tissues through electromagnetic radiation–induced rotation of dipole molecules, such as water, resulting in frictional heat.[24] MWA generates higher temperatures than RFA in a short time leading to larger ablation zones and less susceptibility to heat-sink effects of adjacent blood vessels.[25] Unlike RFA, MWA can be effective in tissues with high impedance such as charred desiccated tissue.[25]

Due to its novelty, only a few articles have been published regarding MWA of IHC. The largest study retrospectively reviewed 107 patients with 177 primary or recurrent IHC who underwent MWA.[26] In this study, all tumors were smaller than 5 cm and number of tumors was three or less per patient. They demonstrated OS survival at 1, 3, and 5 years of 93.5, 39.6, and 7.9%, respectively. Similar to RFA,[13] lower number of tumors was associated with longer OS.[26] Yu et al reported 60% survival at 1 and 2 years in 15 patients following MWA of IHC.[27] Xu et al examined percutaneous MWA versus surgical resection for recurrent IHC.[28] In a total of 121 patients, there was no significant difference in 5-year OS for the MWA group versus the surgical resection group (23.7 vs. 21.8%). In addition, the patients who underwent MWA had lower performance status than the patients who had surgical resection (mean Karnofsky performance status score of 35 vs. 60). They also demonstrated that the surgical group had significantly longer procedure time, higher blood loss, longer hospitalization time, higher complication rate, and higher cost compared with the MWA group.[28] A retrospective study that combined MWA with simultaneous transarterial conventional chemoembolization using oxaliplatin, gemcitabine, and lipiodol with gelatin sponge in 26 patients demonstrated 6-, 12-, and 24-month survival in 88.5, 69.2, and 61.5% of patients, respectively.[29] These findings suggest a possible benefit of combining locoregional therapies.

There were three studies that combined the results of RFA and MWA. A study of 18 patients with primary or recurrent IHC who underwent RFA and MWA reported OS rates at 6, 12, 36, and 60 months of 66.7, 36.3, 30.3, and 30.0%, respectively. This study reported that primary IHC had a survival advantage over recurrent IHC; a median OS was 29.3 versus 6 months. In addition, the univariate analysis found that the number of tumors did not influence OS.[30] Zhang et al retrospectively compared thermal ablation (RFA and MWA) to repeat hepatic resection in 109 patients with recurrent IHC.[31] Seventy-seven patients had RFA or MWA and 32 patients underwent repeat resection. The median OS at 1, 2, and 3 years was not significantly different between the ablation (69.8, 37.3, and 20.5%, respectively) and surgical (83.8, 38.0, and 17.1%, respectively) groups ($p = 0.996$). They further noted that for tumors greater than 3 cm in size, surgical resection had a survival benefit over ablation ($p = 0.037$) but that there was no difference in OS when the recurrent IHCs were less than 3 cm in size ($p = 0.362$).[31] On the other hand, the study of Takahashi et al retrospectively reviewed 50 IHCs in 20 patients with a mean tumor size of 1.8 cm (0.5–4.7).[23] They reported a median OS of 23.6 months and 95, 40, and 32% at 1-, 3-, and 5-year OS, respectively. They did not find correlation between local tumor progression and tumor size but instead showed that superficial tumor location (<1 cm form the liver capsule) was associated with higher rate of local tumor recurrence.[23]

Cryoablation of Intrahepatic Cholangiocarcinoma

Cryoablation leads to cell death due to cell membrane and organelle damage by dehydration and osmotic pressure

changes due to the formation of intra- and extracellular ice crystals.[32]

The ablation probe circulates high pressure argon gas and the cooling mechanism based on the Joule–Thomson effect reaching temperatures as cold as −160 °C. One of the advantages of cryoablation is the visibility of the growing ice ball with ultrasound, CT, and MRI.[33–35] Cryoablation is recommended over heat producing ablation techniques when there is a concern for thermal damage to adjacent, non–target-sensitive structures such as the gallbladder,[36] diaphragm,[37] and large blood vessels.[38] The analgesic property of cold during cryoablation is associated with less intra- and postprocedural pain.[39,40] Heat sink can also affect cryoablation but to a lesser extent compared with RFA.[41] One of the potential major complications of cryoablation is cryoshock which occur 0.3 to 2.0%[42,43] and is characterized by multiorgan failure and disseminated intravascular coagulation.[37]

There are no current studies specifically evaluating the effectiveness of cryoablation for the treatment of IHC. One single-center study reviewed cryoablation of 299 primary and metastatic hepatic tumors; however, only 6 were cholangiocarcinoma.[44] Similarly, another study of cryoablation of hepatic tumors included 39 tumors of which only 3 were IHC.[45] Both studies concluded that cryoablation is an effective treatment option for both primary and metastatic liver tumors, but no survival data were reported for IHC. Further studies focusing on cryoablation of IHC may help demonstrate its role in a select group of patient where resection or other ablative therapies are not possible.

Irreversible Electroporation of Intrahepatic Cholangiocarcinoma

Irreversible electroporation is the newest of the ablation technologies,[46] which, unlike RFA, MWA, and cryoablation, is a non–thermal-based ablation technology. IRE delivers high-voltage electrical current (up to 3,000 V) between probes which creates nanoscale holes (80–490 nm) in the cell membranes.[47,48] The cells within the ablation zone lose the ability to maintain homeostasis which results in apoptotic cell death with narrow zone of transition.[46–48] The high voltage delivered by IRE causes muscular contraction and potentially cardiac arrhythmia. Therefore, IRE must be performed under general anesthesia with complete neuromuscular blockade and electrocardiogram synchronization.[49] Due to its non-thermal quality, IRE can be considered for ablation of central liver tumors and tumors adjacent to sensitive structures (gallbladder, major bile ducts, and bowel loops).[50–52] IRE is not susceptible to "heat sink" from adjacent blood vessels.[46]

There is a sparsity of data regarding IRE for the treatment of IHC. This is likely due to the novelty of IRE and the rarity of unresectable primary or recurrent IHC suitable for the treatment with IRE. A systematic review and meta-analysis of IRE of hepatic tumors included nine studies with 300 patients, but only 21 patients had IHC.[53] While they reported a reduction in tumor size, subgroup analysis of IHC data was not included.[53] A more recent study of IRE for hepatic tumors which were "deemed unsuitable for thermal ablation" had a similar small cohort of 3 IHC out of 59 primary and metastatic liver tumors and IHC was not included in the tumor

Table 1 Summary of current studies

Study	Ablation type	No. patients	No. tumors	Tumor size cm range (median) or *mean or >/< 3 cm	Overall survival 1 year %	Overall survival 3 years %	Overall survival 5 years %	Major complications
Carrafiello G et al[19]	RFA	6	6	1–5.8 (3.8)	–	–	–	0
Kim JH et al[21]	RFA	13	17	0.8–8 (2.5)	85	51	15	1
Giorgio A et al[20]	RFA	10	12	2.4–7 (3.2)	100	83.3	83.3	0
Kim JH et al[22]	RFA	20	29	0.7–4.4 (1.5)	74	–	–	2
Xu HX et al[30]	RFA 12 MWA 6	18	25	0.7–4.3 (2.8)	36.3	30.3	30.3	1
Fu Y et al[13]	RFA	17	26	2.1–6.8 (4.4)	84.6	43.3	28.9	1
Zhang SJ et al[31]	RFA MWA	77	133	>3cm (52 pts) <3cm (25 pts)	69.8	20.5	–	3
Butros SR et al[18]	RFA	7	9	1.3–3.3 (2.3)	100	60	20	0
Takahashi EA et al[23]	RFA 44 MWA 6	20	50	1.8 ± 1.3	–	–	–	0
Yu MA et al[27]	MWA	15	24	3.2 ± 1.9	60	–	–	3
Yang GW et al[29]	MWA	26	39	3.6 ± 1.1	69.2	–	–	0
Zhang K et al[26]	MWA	107	171	>3cm (49 pt) <3cm (58 pts)	93.5	39.6	7.9	3
Xu C et al[28]	MWA	56	56	2.7 ± 0.5	81.2	42.5	23.7	2

*When median was not available mean or size grouping of >/< 3cm was presented.

type grouping data used to compare outcomes.[54] The non-thermal technology offered by IRE may be advantageous in treating primary and recurrent IHC in patients where the tumor is located adjacent to sensitive structures.

Society Guidelines for Intrahepatic Cholangiocarcinoma Ablation

The current guideline from the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines recommends complete resection as the only potentially curative treatment for patients with IHC (https://www.nccn.org/professionals/physician_gls/pdf/hepatobiliary.pdf). Ablation is not considered among the treatment options of IHC. By contrast, the European Association for the Study of the Liver (EASL) recommends ablation for single lesions of 3 cm and smaller if surgery is not an option. However, it emphasizes the need for randomized control trials to better define the role of ablation in IHC.[2]

Conclusion

Intrahepatic cholangiocarcinoma represents a small portion (<10%) of primary hepatic tumors and only small percentage of these patients are candidate for percutaneous ablation treatment.[3] This is the main reason why there are no large studies evaluating the role of ablation in the treatment of IHC (see ►**Table 1** for summary of recent studies). The varying morphology and infiltrative growth pattern of IHC and the late stage at which it is diagnosed continue to make it challenging to effectively treat. Ablation appears to be of most benefit in the setting of tumors 3 cm and smaller. Ablative therapies may also benefit patients with comorbidities or advanced age who are poor surgical candidates. It has been suggested that because of the infiltrative characteristic of IHC, wider ablation margins of at least 10 mm should be created around the tumor.[13,55] New ablative technologies, such as IRE, allow for treatment of IHC adjacent to sensitive structures expanding the role of ablation in the treatment of IHC. Percutaneous ablation has low complication rate, lower cost, and shorter length of hospital stay compared with surgery,[12] while the efficacy is the same in tumors of 3 cm in size or smaller.[31] Combining ablation with embolization may have added survival benefit for IHC patients.[29] Given the poor prognosis[1,5] and low candidacy for surgical resection,[9] ablative therapies for IHC offer an effective treatment alternative for primary and recurrent IHC in patients who are unresectable or poor surgical candidates.

Conflict of Interest
None declared.

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