Thermal ablation of intrahepatic cholangiocarcinoma: a narrative review

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Contributions: (I) Conception and design: All authors; (II) Administrative support: None; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Abstract: Intrahepatic cholangiocarcinoma (ICC) is an aggressive tumor that often presents at a late stage and frequently occurs in patients with underlying liver disease. Due to these factors, most patients are ineligible for curative surgical resection at presentation. Additionally, most patients that undergo curative intent surgery nonetheless develop recurrent disease. Consequently, there is increasing interest in using other local therapies to treat unresectable primary cancers as well as recurrent disease following resection. Thermal ablation is a well-established method for the treatment of a variety of primary and metastatic tumors of the liver. It provides high rates of local tumor control and may be curative in early-stage tumors. It can be performed minimally invasively, with high technical success and low rates of complications, even in patients unfit for surgical resection. However, a detailed understanding of patient anatomy, tumor biology, and ablation technology are required to achieve optimal results. In this review, we summarize the data regarding the outcomes of thermal ablation for ICC. We review the necessary technical and clinical considerations in patients undergoing thermal ablation. We address several challenges of this therapy, including potential complications, and discuss strategies to mitigate risk and improve outcomes. We also discuss ongoing controversies and areas for potential future investigation.

Keywords: Cholangiocarcinoma; ablation; liver

Received: 10 February 2021; Accepted: 04 March 2021; Published: 30 March 2021.
doi: 10.21037/dmr-21-15
View this article at: http://dx.doi.org/10.21037/dmr-21-15

Introduction

Intrahepatic cholangiocarcinoma (ICC) represents approximately 5–20% of liver malignancies and carries a poor 5-year overall survival rate of 5% (1). While many cases are sporadic, known risk factors include primary sclerosing cholangitis, metabolic syndrome, alcohol abuse, viral hepatitis, and cirrhosis (1). Because ICC may grow unrecognized until lesions are large enough to cause obstructing jaundice, many patients are diagnosed at a late stage and often with high-grade disease. Of those patients with more limited disease, many present with underlying hepatic dysfunction such as cirrhosis, and will not be candidates for major surgical resection (2). Ultimately, only approximately one third of patients with ICC will be candidates for resection at presentation (1,3,4). Furthermore, even in patients who are able to undergo liver resection, recurrence rates may be as high as 70% (5,6). Repeated resection after postoperative recurrence is often limited, due to the size of the liver remnant or presence of multifocal recurrence (7).

Systemic therapy offers modest benefit to patients with ICC, with median progression-free survival of 8 months and an overall survival of 11.7 months (8). Unfortunately, tolerance to chemotherapy remains a problem, with grade III/IV toxicities occurring in up to 70% of patients (8). Given all of these limitations, liver-directed therapies such as thermal ablation may play an important role in the treatment of patients with both primary and recurrent ICC.

Thermal ablation is a well-established method for the treatment of a variety of primary and metastatic tumors. It provides high rates of local tumor control and may be curative in several early-stage tumors such as lung, hepatocellular, and renal cell carcinoma (9-12). It can be performed minimally invasively, with high technical success and low rates of complications, even in patients unfit for surgical resection. Given the high rates of morbidity and mortality due to liver progression in patients with ICC, thermal ablation may serve a particularly important function in limiting intra-hepatic tumor progression and preventing liver failure (7). We present the following article in accordance with the narrative review checklist (available at http://dx.doi.org/10.21037/dmr-21-15).

Most previous reports of thermal ablation for ICC have utilized either radiofrequency (RF) or microwave (MW) technology. These technologies are similar, in that both utilize extreme temperatures in excess of 60 degrees centigrade to induce coagulative necrosis and cell death. However, these technologies differ in their method of energy delivery and tissue heating, which results in several key clinical distinctions. In RF ablation, a probe is placed within a volume of tissue and is used to generate a rapid alternating electrical current. As the current travels through the tissue, local frictional agitation generates heat around the RF probe, resulting in a rise in tissue temperature (13). The heat then propagates through thermal conduction to cause a well-defined area of tissue destruction. Because RF relies on both electrical and thermal conduction to cause tissue necrosis, variations in tissue characteristics, such as tissue water content and blood flow, can greatly impact RF ablation zones (14,15). Similarly, because of the relatively lower temperatures achieved with RF, adjacent blood vessels can cause local cooling effects that limit thermal conduction and lead to less predictable and effective ablation zones (16).

In contradistinction to RF, MW spectrum energy causes local tissue heating by means of frictional energy generated from water molecule oscillation. As a result, MW ablation does not rely on electrical conductivity and is therefore much less susceptible to local tissue characteristics. Furthermore, MW relies primarily on active tissue heating, rather than tissue conduction, to produce cellular death. This can allow for more uniform heating, higher temperatures, and larger ablation zones (17,18). Additionally, unlike RF, where multiple applicators may cause electrical interference, multiple MW probes may be combined to produce larger, confluent ablation zones (19-21). Although these factors may facilitate improvement of ablation zones, they potentially increase the risk of the procedure. Due to the increased size and temperature of the ablations performed with MW, there is a potential for increased risk of non-target ablation injuries to adjacent structures and subsequent complications.

Thermal ablation of ICC

RF ablation for ICC was first described in 2002 (6). To date, published literature consists primarily of small, retrospective studies. *Table 1* summarizes fifteen case series of thermal ablation in ICC between 2005 and 2020. Several general observations can be made regarding the published data. Firstly, due to the rarity of this malignancy, most of the reports consist of relatively small populations of patients. Additionally, the majority of the reports are comprised of a mixed population of both primary ICC and recurrent ICC following prior resection, with two of the studies reporting outcomes exclusively in patients with recurrent ICC (24,27). Although this complicates the interpretation of the outcomes reported, studying recurrent cholangiocarcinoma is particularly important, as many patients will experience intraparenchymal recurrence following surgery (22,24). Finally, treatment modalities, parameters, and outcome measurements vary between studies, making comparisons between each study difficult.

Outcomes following ablation

Most of the literature confirms the high technical success of ablation for the treatment of ICC. Assessment of technical success is typically performed by imaging evaluation with either ultrasound or CT scan at 1 month following ablation. Commonly, the ablation is deemed successful if there is complete necrosis within the treated tumor without evidence of tumoral or peri-tumoral enhancement (2). Among the case series, technical success was ≥80% in 12 series and ≥90% in 6 series.

Without treatment, median survival for ICC is 3.9 months (4). An estimate of median overall survival of among patients receiving non-surgical palliative treatments, excluding ablation, such as chemotherapy, radiation, and transarterial chemoembolization is 12.9 months (5). Twelve

Table 1 Summary of case series reporting outcomes of patients treated with thermal ablation for intrahepatic cholangiocarcinoma

Study	No. of pts	% recurrent	Ablation modality	Technical success (%)	Complication rate (%)	1YS (%)	5YS (%)	mOS (months)
Chiou *et al.* 2005; (2)	10	0	RF	80	10	–	–	–
Carafiello *et al.* 2010; (3)	6	0	RF	66	0	–	–	–
Fu *et al.* 2011; (22)	12	100	RF	94.7	5.6	87.5	–	30
Giorgio *et al.* 2019; (23)	10	10	RF	60	0	100	83.3	–
Kim *et al.* 2011; (7)	13	0	RF	88	6	85	15	38.5
Kim *et al.* 2011; (24)	20	100	RF	97	7	95	–	27.4
Yu *et al.* 2011; (25)	15	0	MW	87.5	20	60	–	10
Haidu *et al.* 2012; (26)	11	18	RF	92	13	91	–	60
Fu *et al.* 2012; (27)	17	59	RF	96	3.6	84.6	28.9	33
Xu at al. 2012; (4)	18	56	RF/MW	92	5.5	36.3	30.3	8.8
Butros *et al.* 2014; (28)	7	86	RF	89	0	100	20	38.5
Zhang *et al.* 2018; (29)	107	56	MW	89	2.8	93.5	7.9	28.0
Takahashi *et al.* 2018; (5)	20	76	RF/MW	100	0	–	–	23.6
Giorgio *et al.* 2019; (30)	71	NR	RF/MW	–	0	88	45	–
Diaz-Gonzalez *et al.* 2020; (1)	27	0	RF/MW	85.2	7.4	88.9	14.8	30.6

1YS, 1-year overall survival; 5YS, 5-year overall survival; mOS, median overall survival; RF, radiofrequency; MW, microwave.

of the studies of thermal ablation for ICC report survival data. The 1-year overall survival in these reports range from 36–100%, with 10 of the studies reporting a >85% 1-year survival. Five-year survival was reported in 8 of the studies and ranged from 8–83%, with 6 of the studies reporting 5-year survival of <31%. The median overall survival after thermal ablation of ICC among the 11 studies reporting was 30 months, with a range 8.8–60 months. These data suggest that there can be a meaningful prolongation of survival for select patients with ICC with the addition of thermal ablation.

Complications

Complication rates following thermal ablation of ICC occur in a minority of patients, with a reported range of 5–10%. Most risks and complications of thermal ablation for ICC are similar to those of thermal ablation for other liver tumors. These included hemorrhage, infection, vascular injury or thrombosis, and non-target ablation injury to adjacent organs or structures. Commonly, patients may also experience mild symptoms of fatigue, myalgias, pain, and low-grade fever, which are generally referred to as "post-ablation syndrome." This is typically self-limiting and treated with analgesics and anti-inflammatory medications. However, several rare complications require special attention when discussing thermal ablation of ICC. Due to the intimate relationship between the tumor and adjacent bile ducts, biliary stricture, biloma, and bile leak may occur following thermal ablation. Special care must be taken to ensure the ablation zone does not encompass any major central biliary structures. Additionally, while infections are a potential risk of any thermal ablation, patients with ICC are potentially at increased risk of infectious complications. Given the higher rate of biliary obstruction in this population, many patients will have undergone prior biliary interventions such as ERCP or biliary stenting. These procedures allow bacterial colonization of the biliary tree and are known to increase the risk of hepatic infection and abscess formation (31). Therefore, any patients with this history require extended prophylactic antibiotics to mitigate this complication.

Special considerations

Tumor size must be considered when planning thermal ablation of ICC. Historically, based primarily on data from hepatocellular carcinoma, ablation has generally been limited to patients with tumors ≤3 cm. While technical advances have improved the ability to treat larger tumors, most series of thermal ablation for ICC described diminishing technical success with larger tumors (7,20,23,24). For example, Chiou *et al.* reported 100% efficacy for tumors <3 cm, with decreasing efficacy in tumors 3–5 cm (2). However, it should be noted that the majority of the studies analyzed the use of RF ablation, which is known to be limited in its ability to create large ablation zones. Therefore, it is possible that the use of MW ablation, and particularly multi-probe ablation, may improve upon these results (5). Two previous studies attempted to directly compared RF to MW ablation (5,30). Giorgio *et al.* performed a multicenter retrospective review of 71 patients with 98 primary and recurrent ICC lesions. They demonstrated improved disease-free and overall survival in patients treated with MW ablation compared to RF ablation. Additionally, this benefit persisted in patients with tumors up to 4 cm in size (30). In contrast, Takahashi *et al.* found no difference between RF and MW ablation in a study of 20 patients with 50 ICC lesions. However, the mean size of lesions in this study was 1.8 cm and 88% of patients were treated with RF, which may limit the study's ability to identify a difference between the modalities (5).

Several of the unique features of ICC may present challenges for thermal ablation. Compared with metastatic disease and primary hepatocellular carcinoma, ICC frequently has ill-defined borders and commonly demonstrates infiltrative growth on imaging. Pathologically this correlates with irregular or "rolled" tumor borders and frequently peritumoral satellites (27). These features may lessen the ability to achieve an adequate ablation that encompasses all tumor, and may increase the risk of post-ablation recurrence (4). Due to the infiltrative nature of ICC, it has been proposed that a larger ablation zone may be necessary to ensure complete tumor eradication, and an ablation margin of ≥1 cm may be needed (27). Furthermore, the approximation of the tumor to other intraperitoneal structures, such as the colon and duodenum, can further add complexity to the treatment. Previous reports have shown that, compared to tumors deep within the parenchyma, superficial ICC lesions are associated with earlier local tumor progression after ablation. This is likely due to the inability to safely achieve an adequate ablation margin (5). While these features may increase the technical challenges of performing ablation of ICC, several methods may be used to mitigate them. As stated previously, multi-probe MW ablation can achieve large ablation zones in a single session, often in excess of 5 cm, and can help ensure an adequate margin. Furthermore, for very large tumors, pre-ablative arterial embolization can work synergistically with ablation to treat the tumor, decrease heat dispersion, and help increase the volume of ablation (3). Finally, for tumors near the liver surface, numerous techniques may be employed to help minimize the risk of adjacent organ injury. These include air or hydro-dissection, balloon protection, and open or laparoscopic assistance.

Despite the high initial technical success of thermal ablation for ICC, metastatic tumor recurrence remains common, with a median time to recurrence of 10.1 months (1). Increased risk of recurrence may be due to several factors, though the evaluation of these factors is limited by the retrospective nature of the available data. Predictors of poor outcome include lymphovascular invasion, periductal infiltrating disease, elevated CA 19-9, lymph node metastasis, and poorly differentiated histology (27). Therefore, these factors should be evaluated in all patients being considered for ablative therapy.

Given the underlying liver dysfunction in many patients with ICC, there should be careful consideration of hepatic reserve when evaluating potential candidates for treatment. Based on the extensive available literature in hepatocellular carcinoma, most practitioners consider patients with mild to moderate liver dysfunction to be acceptable candidates for thermal ablation. Furthermore, Diaz-Gonzalez *et al.* examined ablation of ICC exclusively among patients with cirrhosis and found no specific safety concerns (1).

Finally, there remains controversy regarding which patients with recurrent cholangiocarcinoma may be best served by repeat resection versus ablation. Repeat hepatectomy can be technically challenging, but median survival after repeat hepatectomy has been reported to be as high as 20 months (32). To answer this question, Zhang *et al.* retrospectively compared 109 patients with recurrent ICC who had undergone either repeated hepatic resection or thermal ablation. They found no difference in overall survival among those patients with tumors less than 3 cm. Additionally, major complications were significantly higher in patients who underwent repeat hepatic resection (33).

Conclusions

ICC is a challenging cancer with poor prognosis. Many patients are ineligible for curative intent surgical resection, yet most patients who go without any treatment will not survive beyond 6 months. Thermal ablation is an effective treatment for select patients with limited primary or recurrent disease. Additionally, thermal ablation has low rates of complications and may be performed safely in patients who are poor candidates for other treatments. Patients with limited, small, and well-circumscribed tumors likely benefit most from this treatment. Broader adoption of contemporary MW ablation devices may further improve outcomes.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the Guest Editor (Yi-Jen Chen) for the series "Locoregional and systemic treatment in intrahepatic cholangiocarcinoma" published in *Digestive Medicine Research*. The article has undergone external peer review.

Reporting Checklist: The authors have completed the narrative review checklist. Available at http://dx.doi.org/10.21037/dmr-21-15

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/dmr-21-15). The series "Locoregional and systemic treatment in intrahepatic cholangiocarcinoma" was commissioned by the editorial office without any funding or sponsorship. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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doi: 10.21037/dmr-21-15
Cite this article as: Thornblade LW, Kessler J. Thermal ablation of intrahepatic cholangiocarcinoma: a narrative review. Dig Med Res 2021;4:11.

