Minimally Invasive Locoregional Treatment of Intrahepatic Cholangiocellular Carcinoma

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ABSTRACT
Surgical resection is considered first-line treatment for intrahepatic cholangiocellular carcinoma (ICC). In case of an unresectable tumor, chemotherapy is part of standardized treatment guidelines, despite dismal outcome. Technical advances in locoregional therapies such as radiofrequency ablation, microwave ablation, irreversible electroporation, transarterial chemoembolization and selective internal radiation therapy bear the promise for enhancing local tumor control, while reducing treatment associated morbidity and improving survival as well as quality of life. This review focuses on the latest improvements of minimally invasive locoregional therapies and their implementation in modern multimodality treatment protocols for ICC.

Key words: radiofrequency ablation, cholangiocarcinoma, hepatic liver tumor treatment, thermal ablation

INTRODUCTION
Cholangiocarcinomas arise from the epithelial cells of bile ducts, forming intrahepatic or extrahepatic neoplasms, and are the second most common primary liver malignancy, accounting for 10 to 15% of liver malignancies diagnosed worldwide (1, 2). Approximately 5 to 10% of cholangiocarcinomas are intrahepatic (3).

Intrahepatic cholangiocellular carcinomas (ICCs) can originate from either small intrahepatic ductules (peripheral ICCs) or large intrahepatic ducts proximal to the bifurcation of the right and left hepatic ducts. ICC tumor growth patterns include the mass-forming type, the periductal-infiltrating type with associated intrahepatic ductal dilation, and a mixed type. The purely mass-forming type is most common, accounting for approximately 60% of all ICCs, whereas the purely periductal and mixed types account for approximately 20% of cases each (4).

ICCs are frequently diagnosed in an advanced stage of disease. They progress rapidly and lead to biliary obstruction and liver failure. Surgery is the established standard treatment approach (5). Resectability rates for ICCs have increased over time, due in part to more aggressive operative strategies and...
broadened criteria for resectability (6). However, the majority of cases recur despite potentially curative R0 resection (7-13), leading to a recurrence rate of up to 70% (14). The median overall survival after surgical resection is 18 to 30 months (15). One third of patients are still unresectable (16).

Kolarich performed a retrospective analysis of the treatment strategies in 6140 patients with ICC diagnosed in the United States between 2004 and 2015. Only 29% of these patients were surgical candidates, and in the subgroup of the remaining patients with stage I disease RFA was the only treatment strategy with improved survival (17). Orthotopic liver transplantation (OLT) is not considered to be a standard therapeutic approach for localized cholangiocarcinoma (18).

To date, no prospective trials are available about the value of adjuvant external beam radiation therapy after local curative resection, and results from retrospective studies are contradictory.

Chemotherapy and radiation therapy did not succeed in significantly increasing the long term survival in unresectable patients. The preferred chemotherapeutic regimen consists of a combination of gemcitabine and cisplatin and results in a median progression-free survival (PFS) of 8 months and a median overall survival (OS) of 12 months (19). Studies evaluating this combination reported a survival benefit of 8 months over gemcitabine monotherapy (20, 21). However, current guidelines indicate that radiotherapy and selective internal radiation therapy (SIRT) may be considered as second line treatments after chemotherapy (22).

In this article we review current strategies of minimally invasive locoregional treatment of ICC.

MINIMAL INVASIVE LOCOREGIONAL TREATMENT APPROACHES

Transarterial therapies

Transarterial embolisation (TAE), transarterial chemoembolisation (TACE) and SIRT are highly selective treatment options for ICC. For TACE combines a mixture of lipiodol and chemotherapeutic agents such as doxorubicin, gemcitabine, mitomycin or epirubicin. Drug eluting bead TACE (DEB-TACE) uses embolizing beads that are loaded with chemotherapeutic agents.

DEB-TACE results in similar overall survival as compared to conventional TACE. Whether TAE or TACE is superior has not yet been shown in randomized, controlled trials (23). TACE has led to prolonged survival (12.2. months) in 155 patients suffering from unresectable ICC in comparison to best supportive care (3.3 months)(24). In 2013, a metaanalysis of hepatic artery-based therapies for unresectable ICC found a median overall survival of 15.7 months from diagnosis and 13.4 months from therapy (25). TACE in combination with systemic therapies has shown to prolong survival. In a systematic review, including 13 studies with 504 ICC patients undergoing TAE therapies using chemotherapeutic agents or radiation, the progression-free survival ranged from 1.8 to 10 months, and the 1-, 2- and 3- year survival rates were 38-78%, 12- 38% and 4-30% (26).

Transarterial selective internal radiotherapy (SIRT) is performed using Yttrium-90 glass or resin microspheres. The effect of mechanical embolization is combined with the delivery of biologically highly effective ß-radiation at the tumor site. Results of SIRT in ICC have been summarized in a review, reporting a median survival time ranging from 4.4 to 52 months (27). A systematic review of SIRT in ICC reported a partial response in 28% and stable disease in 54% 3 months postinterventionally, summarizing 12 studies (28).

In a study including 198 patients with ICC undergoing treatment with chemoembolization, bland embolization, or radioembolization, complete or partial radiographic responses in 41 patients were reported, while 99 had stable disease. The median overall survival was 13.2 months and did not differ according to the type of intraarterial therapy (29).

Local ablative treatment

Ablative procedures include radiofrequency ablation (RFA), microwave ablation (MWA), cryotherapy and irreversible electroporation (IRE). In 2002, the first case of RFA in ICC was published by Slakey et al., combining ablation and surgery in recurrent disease after liver surgery (30). Case reports confirming these first finding followed in the following years (31-33). In 2012, Bale and coworkers reported on the advantage of stereotactic RFA, allowing precise multiplanar planning of RFA even in large sized tumors. A median overall survival of 60 months was reached, making stereotactic RFA an alternative to resection (34).

In recurrent ICC, multifocal tumor and restricted liver function are immanent clinical problems requiring safe and technically advanced treatment options (35). RFA is a well established local treatment option based on high frequency alternating current, that can be performed under local anesthesia or general anesthesia. Contraindications for RFA include central bile duct invasion, biliodigestive anastomosis and
clinically relevant coagulation disorders. Probes are placed under computed tomography (CT)-, ultrasound (US)-, or magnetic resonance tomography (MRI)-guidance. Local tissue heating of up to 100° is achieved in the tissue adjacent to the non-isolated part of the probe, leading to coagulation necrosis. Needle placement and ablation duration are at the discretion of the performing radiologist, such that the ablation zone covers the tumor with a safety margin of at least 1 cm or greater.

Complete ablation of the tumor is confirmed in the control imaging at the end of the intervention, allowing for reinsetion and repeat ablation, if necessary. Histopathologic studies have confirmed that local curative treatment can be reached by RFA if an ablation margin of 1 cm of healthy tissue surrounding the tumor is achieved (34).

Follow up imaging after local treatment includes CT and MRI 3 to 6 months postinterventionally or according to clinical needs during the postoperative period. Evaluation of images is performed to standardized criteria following ablation (36).

RFA combines a highly effective treatment approach with favorable results, with low morbidity and mortality rates (table 1). A non-controlled metaanalysis including 3670 patients reported a complication rate of 8.9% and a mortality rate of 0.5% (37). However, the technical approach to RFA varies widely, leading to heterogeneous results in technical success and tumor recurrence rate after RFA. US guided RFA has shown to be feasible in tumors smaller than 3 cm. However, in tumors larger than 3 cm, 3 out of 7 tumors could not be ablated completely (38). These results are not equal to reports on RFA using conventional CT guidance for needle placement. A progression free survival of 32.3 months and a median survival of 38.5 months was reached, with 1-, 3- and 5-year survival rates of 85, 51 and 15% (39,40).

Microwave ablation (MWA) is based on creation of an electromagnetic field creating heat in the tumor tissue. It has also shown to be an effective local treatment approach in ICC patients, with a technical success rate of 91.7% (41). Takahashi et al published data on 20 patients with 50 ICCs, who were treated using RFA or MWA between 2006 and 2015, including patients with recurrence of disease after surgery. No significant difference was observed in outcome of RFA and MWA treatment. No major complication occurred. The estimated 1-, 3- and 5-year survival rates were 95%, 40% and 0.32%. Five patients suffered local tumor progression after ablation, with a median time to progression of 7.1 months (42).

Similar reports included 18 and 26 patients, respectively, comparing RFA to MWA alone or MWA in combination with TACE (43, 44). Another study group reported a median overall survival in 105 patients with ICC following RFA and a combination of treatments in a retrospective chart review of 16.1 months (45). Kim et al. reported a longer median overall survival in a group of 20 patients following RFA of ICC with 38.5 months (46), which was confirmed by findings of Fu et al. (47).

Zhang et al. compared survival rates in patients with recurrent ICCs after hepatic resection or thermoablatative treatment, and did not find a significant

### Table 1 - Case control studies reporting results of thermal ablation in primary or recurrent ICC

<table>
<thead>
<tr>
<th>Author (Ref.)</th>
<th>Thermal ablation technique</th>
<th>Year of publication</th>
<th>Number of patients</th>
<th>Number of tumors and size</th>
<th>Mean overall survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bale (59)</td>
<td>SRFA</td>
<td>2013</td>
<td>17</td>
<td>up to 10 cm</td>
<td>60</td>
</tr>
<tr>
<td>Takahashi (42)</td>
<td>RFA, MWA</td>
<td>2018</td>
<td>20</td>
<td>1.8±1.3 cm</td>
<td>23.6</td>
</tr>
<tr>
<td>Zhang (48)</td>
<td>RFA, MWA</td>
<td>2013</td>
<td>109</td>
<td>up to 6.7 cm</td>
<td>21.3</td>
</tr>
<tr>
<td>Carafiello (39)</td>
<td>RFA</td>
<td>2010</td>
<td>6</td>
<td>1 to 5.8 cm</td>
<td>20</td>
</tr>
<tr>
<td>Kim (40)</td>
<td>RFA</td>
<td>2011</td>
<td>13</td>
<td>up to 5 cm</td>
<td>38.5</td>
</tr>
<tr>
<td>Giorgio (57)</td>
<td>RFA</td>
<td>2011</td>
<td>10</td>
<td>2.5 to 3.2 cm</td>
<td>Follow-up of only 19.5 months</td>
</tr>
<tr>
<td>Butros (3)</td>
<td>RFA</td>
<td>2014</td>
<td>7</td>
<td>1.3 up to 3.3 cm</td>
<td>38.5</td>
</tr>
<tr>
<td>Fu (47)</td>
<td>RFA</td>
<td>2011</td>
<td>12</td>
<td>1.9 up to 6.8 cm</td>
<td>30</td>
</tr>
</tbody>
</table>
difference in tumors with a size below 3 cm. The 1-, 2- and 3- year overall survival rates were 69.8, 37.3 and 20.5% for RFA patients, with no significant difference to patients undergoing surgery (48). Kamphues et al. reported a series of 13 patients undergoing liver resection in combination with RFA of ICC, and found both approaches to be safe and effective, with an overall survival of 51 months (49).

The pooled 1-, 3- and 5- year overall survival rates reported in a metaanalysis including 7 studies for outcome of RFA in ICCs are 82%, 47% and 24%. RFA prolonged survival even in unresectable ICC patients. However, technical success rates varied between 88 and 100% and technical effectiveness rates varied between 66 and 96.2%. Major complication rates were low, between 0 and 8.3% (50). Possible complications of RFA include hepatic failure, bleeding, liver abscess, pneumothorax, bowel perforation. A study comparing liver resection to RFA in ICC reported a higher rate of major complications after surgery than in the RFA group, with 46.9% vs. 3.9% (48).

**Stereotactic radiofrequency ablation**

Stereotactic Radiofrequency Ablation (SRFA) combines the advantages of local ablative treatment and precise needle placement using a 3D- planning software, patient immobilisation devices, aiming devices, tube disconnection during needle placement and muscular blockade. It facilitates a multiple needle approach and precise tumor ablation even in unresectable tumors. It allows for precise placement of multiple probes, creating overlapping coagulation necrosis. In contrast to conventional ultrasound and CT guided single probe ablation, SRFA allows for effective treatment of large ICCs (51-57).

The 3D navigation system is used to visualize the needle position in real time in relation to preoperatively aquired CT, MRI, SPECT or PET image data sets. The needle pathways can be adopted accordingly. The size of the necrosis depends on the distribution of heat from the electrode tip to the periphery of the tumor, as well as on the blood flow at the site of ablation, leading to the so called heat sink effect. This effect can be overcome by increased duration and power of ablation, with ablation probes being preferentially positioned in the region of the tumor next to the vessel site. Needle placement is performed with high accuracy. A median lateral error of needle placement of 2.5 mm was reported (58). Haidu et al. reported a 1- and 3- year survival rate of 91% and 71% in 11 patients after SRFA (34), with an estimated median overall survival of 60 months. Tumor size did not influence overall survival. No patient died perioperatively and the morbidity rate was 13.8% (59).

**Irreversible electroporation**

Irreversible electroporation (IRE) is a non-thermal image-guided ablation technique based on creating short-pulsed high- voltage current fields, inducing cellular apoptosis. The electrical pulses permeabilise the lipid bilayer of the cell membrane, hereby disrupting intracellular homeostasis and inducing apoptosis. Due to the non-thermal mechanism, the method is causing less damage to surrounding tissue, especially when probes are positioned next to bile ducts, hereby overcoming limitations of the before mentioned ablation techniques. The number of probes used for ablation depends on tumour size and shape. A recently published metaanalysis on treatment of hepatic malignant tumors with IRE reported a significant reduction in tumor diameter, but no survival data is available so far (60).

**Cryoablation**

Despite the fact that cryoablation represents a valuable tool in thermal ablation therapies, no study group has yet investigated the role in treatment of cholangiocellular carcinoma, yet. In cryoablation, specific ablation probes are applied, using argon or helium gas to freeze tissue, creating an ice ball predefined by the given probe. The treatment effect can be directly monitorized by visualization of the ice ball. A variety of cryoablation probes is available, in order to create the appropriate ice ball necessary to cover the tumor target. Nevertheless, the first studies on cryoablation reported a significant number of adverse events in comparison to other thermal ablation techniques (61). In addition, the technical issue on needle tract ablation has not been solved yet for cryoablation probes, increasing the risk of tumor seeding.

**OUTLOOK**

Despite surgery being listed as the standard treatment approach for ICC, this rare and aggressive liver neoplasm is often managed non-surgically, as local ablative techniques are currently improving, enabling local tumor control in combination with low morbidity and mortality rates. Especially in patients suffering a more advanced stage of disease and liver function
restriction, or in elderly patients, feasible and effective local treatment approaches have the potential to improve survival and quality of life. Although multiple therapeutical approaches are available for locoregional therapy of ICC, prospective randomized controlled trials for treatment effectiveness are not yet available. Controlled case series and metaanaylses are available for local ablative therapies and TACE. Heterogeneous patient populations and inconsistent therapeutic regimens hamper a comparison of available data. RFA is a safe and highly effective treatment option, resulting in a potential survival benefit and improving the quality of life of ICC patients in comparison to chemotherapy or best supportive care. Due to its minimal invasiveness and at least equal local control rates to surgical resection multiprobe stereotactic RFA challenges surgery as first line treatment in ICC.

CONCLUSION

Minimally invasive thermal ablation methods represent potentially local curative treatment approaches for ICCs. RFA offers a safe and oncologic feasible alternative to surgery, being associated with a significantly lower complication rate and less loss of liver parenchyma as compared to hepatic resection. In contrast to conventional ultrasound- and CT-guided RFA, multiprobe stereotactic RFA allows for treatment of more complex and larger liver tumors, by using 3D navigation systems and image registration techniques. Future trials should focus on a combination of locoregional ablation techniques and systemic treatment for possible improvement in survival. The future holds the promise of more complex multimodal treatment concepts for CCA patients to improve overall survival and quality of life.

Conflict of interest

All author declare that they have no conflict of interest.

REFERENCES


