Locoregional Therapies of Cholangiocarcinoma

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Keywords

Cholangiocarcinoma · Radiofrequency ablation, RFA · Microwave ablation, MWA · Hepatic artery infusion, HAI · Transarterial chemoembolization, TACE · Transarterial radioembolization, TARE

Summary

Background: Cholangiocarcinoma (CC) is the second most primary liver malignancy with increasing incidence in Western countries. Currently, surgical R0 resection is regarded as the only potentially curative treatment. The results of systemic chemotherapy and best supportive care (BSC) in patients with metastatic disease are often disappointing in regard to toxicity, oncologic efficacy, and overall survival. In current practice, the use of different locoregional therapies is increasingly more accepted.

Methods: A review of the literature on locoregional therapies for intrahepatic cholangiocarcinoma (ICC) was undertaken. **Results:** There are no prospective randomized controlled trials. For localized ICC, either primary or recurrent, radiofrequency ablation (RFA) is by far the most commonly used thermal ablation modality. Thereby, a systematic review and meta-analysis reports major complication in 3.8% as well as 1-, 3-, and 5-year overall survival rates of 82, 47, and 24%, respectively. In selected patients (e.g. with a tumor diameter of ≤ 3 cm), oncologic efficacy and survival after RFA are comparable with surgical resection. For diffuse ICC, different transarterial therapies, either chemotherapy-based (hepatic artery infusion (HAI), transarterial chemoembolization (TACE)) or radiotherapy-based (transarterial radioembolization (TARE)), show extremely promising results. With regard to controlled trials (transarterial therapy versus systemic chemotherapy, BSC or no treatment), tumor control is virtually always better for transarterial therapies and

very often accompanied by a dramatic survival benefit and improvement of quality of life. Of note, the latter is the case not only for patients without extrahepatic metastatic disease but also for those with liver-dominant extrahepatic metastatic disease. There are other locoregional therapies such as microwave ablation, irreversible electroporation, and chemosaturation; however, the current data support their use only in controlled trials or as last-line therapy. **Conclusion:** Dedicated locoregional therapies are commonly used for primary and recurrent ICC as well as liver-only and liver-dominant extrahepatic metastatic disease. Currently, the best evidence and most promising results are available for RFA, HAI, TACE, and TARE. In cohort studies, the overall survival rates are similar to those obtained with surgery or systemic therapies. Prospective randomized controlled trials are warranted to compare safety and efficacy between different surgical, interventional, and systemic therapies, as well as their combinations.

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Introduction

The aim of this review is to summarize the data on the different locoregional therapies for cholangiocarcinoma (CC), including indications, patient selection, technical effectiveness, complications, and adverse events as well as oncologic efficacy and survival. PubMed was the source for primary selection, whereby publications were extracted by using a search algorithm with the following medical subject heading terms and text words: ‘cholangiocarcinoma’, ‘radiofrequency ablation’, ‘microwave ablation’, ‘hepatic artery in-

fusion', 'transarterial chemoembolization', and 'transarterial radioembolization'. Additional publications were identified after cross-checking of the reference lists of the articles extracted by means of primary selection. A description of the different modalities and techniques available for locoregional therapy is not outlined in this overview; however, it can easily be obtained from other publications [1–10].

Locoregional Therapy

Thermal Ablation

Radiofrequency Ablation

A summary of the published data is presented in supplementary table 1 (available at <http://www.karger.com/ProdukteDB/produkte.asp?doi=453010>). In a recent systematic review and meta-analysis, the outcome after radiofrequency ablation (RFA) for unresectable intrahepatic cholangiocarcinoma (ICC) included pooled 1-, 3-, and 5-year overall survival rates of 82, 47, and 24%, respectively, as well as a pooled local tumor progression rate of 21% [11]. The therapy of 133 tumors resulted in seven major complications (inclusive of one grade V complication according to the Clavien-Dindo classification system of surgical complications) or a pooled median major complication rate of 3.8%. The authors concluded that RFA is a therapy that prolongs survival in patients with ICC even in non-surgical candidates. What is striking about the review is that the results of the analyzed original studies are quite heterogeneous, especially with respect to technical success rates (ranging between 88 and 100%), technical effectiveness rates (ranging between 66 and 96.2%), major complication rates (ranging between 0 and 8.3%), local tumor progression rates (ranging between 8 and 50%) as well as median overall survival (ranging between 20 and 60 months) and overall survival rates (e.g. ranging between 21 and 71% for the 3-year overall survival). In the following paragraphs, the relevance of patient source (patients with primary ICC vs. those with recurrent ICC) and tumor stage (e.g. tumor number and size and extrahepatic metastatic disease) are outlined in the context of efficacy.

- RFA for primary ICC: There are three articles reporting on RFA for primary ICC. In the largest series with $n = 13$ patients and $n = 17$ tumors, technical success and technical effectiveness rates were both 100% for tumors with a diameter of 0.8–4.5 cm and for tumor stages between I and IIb (note: tumors were staged according to Aljiffry et al. [12]) [13]. The corresponding median local recurrence-free and overall survival were 22 and 22 months, respectively. Lack of technical success and technical effectiveness occurred only in 2 patients, both presenting with large tumors (7 and 8 cm). One of the patients passed away 3.3 months after therapy, and the other patient survived for 13.7 months. In a study from 2010, for RFA of solitary ICC with a diameter of 1–4 cm, the technical success, technical effectiveness, and overall survival rates were 100% each, and the median overall survival was 20 months [14]. For 2 patients with tumors

larger than 5 cm, however, RFA even in combination with bland transarterial embolization was not effective and resulted in incomplete tumor destruction. Notwithstanding, both patients survived for 18 months, with one of them still being alive at the time of publication. In the third study, the primary technical success, technical effectiveness, recurrence-free survival, and overall survival rates were always 100% for solitary ICC with a diameter of 2.5–3.2 cm [15]. On the contrary, RFA for solitary ICC with a diameter between 4.5 and 7.0 cm always resulted in technical failure even after two RFA sessions. In all cited studies, the major reasons for surgical unresectability were poor hepatic reserve, comorbidity, patient refusal, and/or central tumor location.

- RFA for recurrent ICC: One original RFA study including patients with exclusively recurrent ICC as well as two original RFA studies providing collectives with a high rate of recurrent CC (85.7 and 58.8%) were identified [16–18]. In a series of 20 patients and 29 recurrent CC, the median time to recurrence was 7.4 months, and 60% of the patients showed recurrence within the first year after so-called curative liver resection [18]. The median diameter of the recurrent CC was 1.5 cm. Primary and secondary technical effectiveness rates of percutaneous RFA were 97 and 100%, respectively. The major complication rate was 7%, whereby only grade $\leq$ III complications occurred. The 1-, 2-, and 4-year local progression-free survival rates were 74% each, and the mean local progression-free survival was 39.8 months. Again, tumor size turned out as a relevant predictor for survival, with significantly better local progression-free survival for patients with tumors <1.5 cm compared with those suffering from tumors ≥ 1.5 cm in size ($p = 0.041$). The 1-, 2-, and 4-year overall survival rates were 70, 60, and 21%, and the median overall survival was 27.4 months. Butros et al. [16] published results regarding RFA for small ICC. Accordingly, in the 6 patients with eight tumors, the mean time to recurrence after surgical resection was 13 months, and the mean primary and recurrent tumor diameters were 5.5 and 2.3 cm, respectively. The primary and secondary technical effectiveness rates of postoperative RFA were 87.5 and 100%, respectively, and the major complication rate was 0%. The local recurrence-free survival rate and the overall survival rate were 100%, and the median local recurrence-free survival as well as the median overall survival were 49 months. In the study published by Fu et al. [17], recurrent ICC with a diameter ranging between 1.9 and 6.8 cm were treated with RFA. The negative predictors for a decreased recurrence-free survival and overall survival after RFA were lymph node metastases, poor tumor differentiation, and either multiple tumors or poor tumor differentiation [17].

Microwave Ablation

Only one specific study on microwave ablation (MWA) as monotherapy for ICC was identified (supplementary table 1) [19]. The series included 15 patients and 24 primary ICC with a diameter of 3.2 ± 1.9 cm; all patients underwent ultrasound-guided percutaneous MWA [19]. During the follow-up of 12.8 ± 8.0 months, the

technical success, technical effectiveness, and local tumor progression rates were 91.7, 87.5, and 25.0%, respectively. The major complication rate was 20%; only grade $\leq$ III complications occurred. The 1- and 2-year overall survival rates were 60.0% each. Two further original series report on thermal ablation by means of MWA and RFA [20, 21]. In the first study, 18 patients with primary ($n = 8$) or recurrent ($n = 17$) ICC were ablated, and followed up for 20.5 ± 26.3 months [20]. The technical effectiveness and major complication rates were 92.0 and 5.5%, respectively. The 1-, 3-, and 5-year overall survival rates for the entire collective were 36.3, 30.3, and 30.3%, respectively. For the subgroup of patients suffering from primary ICC, however, the survival was markedly better, with 1-, 3-, and 5-year overall survival rates of 75.0, 62.5, and 62.5%, respectively. The latter can be explained by the fact that patient source (primary vs. recurrent ICC) – but not gender, number of tumors, therapy modality (MWA vs. RFA), complete ablation, or development of recurrence after ablation – turned out as a predictor for overall survival. The second study including MWA and RFA is a retrospective non-randomized controlled trial [21]. Patients with recurrent ICC were treated with either thermal ablation (77 patients with 133 tumors) or repeated surgical resection (32 patients with 44 tumors). The patient demographics were comparable for both study groups. The median disease-free survival as well as the 1- and 2-year disease-free survival rates were not significantly different between both study groups (thermal ablation: 6.8 months, 33.4%, and 19.7%, respectively, vs. repeated surgical resection: 9.1 months, 37.2%, and 14.9%, respectively). In the subgroup analysis, tumor size (≤ 3 vs. > 3 cm) had no impact on the disease-free survival. Also, the median overall survival as well as the 1-, 2-, and 3-year overall survival rates were not significantly different between both study groups (thermal ablation: 21.3 months, 69.8%, 37.3%, and 20.5%, respectively, vs. repeated surgical resection: 20.3 months, 83.8%, 38.0%, and 17.1%, respectively). However, there was a significant survival benefit for the patients with tumors > 3 cm when repeated surgical resection instead of thermal ablation was performed. It is also noteworthy that 46.8% of the included patients received ‘preventive’ transarterial chemoembolization (TACE).

Transarterial Therapies

Hepatic Artery Infusion

A summary of the published data is presented in supplementary table 2 (available at <http://www.karger.com/ProdukteDB/produkte.asp?doi=453010>). The recently published study by Massani et al. [22] reported single-center results on hepatic artery infusion (HAI) for ICC and compared the outcome with the previously reported literature. After placement of the HAI pump in 11 patients, the mean number of therapy cycles was eight. Each therapy cycle consisted of transarterial infusion of different drugs: 25 mg of folinic acid daily, 8 mg of ondansetron, 4 mg of dexamethasone, and 100 mg/m² of each patient’s body surface of oxaliplatin (diluted in 100 ml of 5% saline solution and infused during 5 h) at day 1 as well as 7 mg/kg of each patient’s weight of 5-fluorouracil (5-FU) (diluted

in 100 ml of 5% saline solution and infused with a flow rate of 2 ml/h during 24 h). Although there were no locoregional complications such as cholecystitis or peptic ulceration, the rates for liver decompensation and hand-foot syndrome were 9.1 and 27.3%, respectively. Tumor control (complete and partial response as well as stable disease according to response evaluation criteria in solid tumors (RECIST)) and overall survival rates were 63.6 and 72.7%, respectively. The median overall survival for the entire collective (11 patients), for the patients with HAI only (8 patients), and for those with HAI in combination with subsequent resection (3 patients) was 17.6, 15.3, and 23.6 months, respectively. For the categorization of these data, the authors performed a literature review with specific inclusion and exclusion criteria. For the seven included studies with a total of 588 patients suffering from different malignant tumors (ICC, extrahepatic cholangiocarcinoma (ECC), gallbladder carcinoma, ampulla carcinoma, and hepatocellular carcinoma), pump-related complication rates ranged between 4.5 and 32.4% [23–29]. The toxicity rate reached 32.3% and included also a grade V adverse event (according to the common terminology criteria for adverse events (CTCAE)) [26, 29]. Partial response, stable disease, and progressive disease rates were 7.7 and 81.4%, 41.2 and 100% (only hepatocellular carcinoma, 61.1% for ICC), as well as 0 and 30.8%, respectively [23–25, 28, 29]. It is noteworthy that three original series on HAI for advanced ICC were not mentioned in the above-cited review [30–32]. In two of the studies with a total of 23 patients, repetitive HAI was performed with different regimens including gemcitabine, oxaliplatin, 5-FU, adriamycin, epirubicin, mitomycin C, and/or cisplatin [30, 32]. The tumor control rates were 91.0 and 82.0%, and the overall survival was 9.1 months (median) and 26.0 months (mean). In the third study, Shitara et al. [31] noted the use of HAI with mitomycin C in combination with degradable starch microspheres. After a total of 204 cycles in 20 patients (median maximum tumor diameter: 7.8 cm, median tumor number: 3, extrahepatic disease rate: 85.0%), the tumor response rate was 50.0% and the median overall survival 14.1 months. Grade III/IV toxicity rates for gastroduodenal ulcer, epigastralgia, anorexia, and nausea/vomiting ranged from 5 to 15%. Only one of the seven studies included HAI exclusively for ICC [23]. In the combined phase I and phase II study, HAI was performed with gemcitabine at doses of 600–1,000 mg/m² of each patient’s weight infused during 30 min at day 1, 8, and 15 every 4 weeks for five cycles. According to the analyses, gemcitabine at a dose of 1,000 mg/m² of each patient’s weight was assumed to be the recommended dose; the corresponding grade IV toxicity (according to CTCAE) and objective tumor response rates were 7.7% each, and the median overall survival was 389 days. Additionally, Massani et al. [22] performed a review of systemic chemotherapy studies. The seven analyzed studies included a total of 549 patients with different liver malignancies (ICC, ECC, gallbladder carcinoma, and ampulla carcinoma), inhomogeneous pre-treatments (e.g. surgical resection, radiotherapy, chemotherapy, or radiochemotherapy) and tumor stage (e.g. rate and/or type of extrahepatic metastatic disease), as well as a range of different chemotherapy regimens (e.g. folinic acid, 5-FU, and oxaliplatin (FOLFOX) or folinic acid, 5-FU, and

irinotecan (FOLFIRI)) [33–39]. The listed data include complete response, partial response, stable disease, and progressive disease rates of 0–5.7%, 4.2–39.5%, 23.3–74.0%, and 17.7–29.4%, respectively [33, 34, 36–38]. The toxicity rates ranged between 0 and 75.0%, and the median overall survival was 7.6–27.7 months [33, 36, 37, 39]. The 1-year overall survival rates were listed in two of the six studies (60.0 and 44.4%) and the 2-/3-year overall survival rates only in one other study (32.0/28.0%) [38, 39]. The results of a meta-analysis comparing different transarterial therapies including HAI are presented below in the chapter on transarterial radioembolization (TARE) [40].

Transarterial Chemoembolization

Four review articles analyzed TACE for CC [40–43]. In the first review, Ray et al. [41] included 16 studies with a total of 542 patients undergoing chemotherapy-based transarterial therapy, whereas in all studies – except in the study by Andrasina et al. [44] – repetitive TACE was performed in a typical fashion with transarterial injection of one or more chemotherapeutic agents and one or more embolic agents [41]. After pooling, the tumor control, severe toxicity, 30-day mortality, and 1-year overall survival rates were 76.8, 18.9, 0.7, and 58.0%, respectively. In the systematic review by Yang et al. [43], 13 studies with a total of 504 patients undergoing TACE for unresectable CC were analyzed regarding definition of response (RECIST), overall survival, and toxicity. Under consideration of the listed data, the progressive disease rate was 0–60.0% and the progression-free survival ranged from 1.8 to 10.0 months [45–48]. The 6-month, 1-year, 2-year, 3-year, and 5-year overall survival rates were 64.0–100%, 38.0–78.0%, 12.0–38.0%, 4.0–30.0%, and 0–8.0%, respectively [45, 46, 49–53]. The acuity of toxicity was <30 days in six studies, 10 days in one study, <3 days in two studies, and not indicated in four studies. The overall toxicity rates ranged from 17.0 to 65.0%, whereas grade I/II and grade III/IV toxicity rates (according to the World Health Organization (WHO) toxicity grades) were 38.0–65.0% and 3.0–37.0%, respectively [49–51, 54]. Seidensticker et al. [42] summarized patient and tumor characteristics and the oncologic outcome for different TACE studies on CC. For nine original series with 391 patients, the extrahepatic disease, prior systemic chemotherapy, and prior liver-directed therapy rates were 29.4–54.0%, 19.0–83.3%, and 8.0–41.7%, respectively [47, 48, 51, 55]. The median overall survival for therapy and diagnosis were 12.0–23.0 and 10.0–16.3 months, respectively, and the objective response (complete and partial response) rate ranged from 4% (RECIST) to 80% (mRECIST) [46, 47, 49, 51, 55, 56]. The results of a meta-analysis comparing different transarterial therapies for unresectable ICC including different TACE techniques are presented below [40]. The listed data demonstrate that repetitive TACE is safe and effective for the treatment of liver-only and liver-dominant CC whenever the adequate embolization technique and different embolic and chemotherapeutic agents are used. No more retrospective single-center studies are needed in this context; it is rather time for standardization and randomized trials under consideration of the published promising TACE data.

- Different TACE techniques: There are three different TACE techniques: conventional TACE (cTACE), degradable starch microspheres TACE (DSM-TACE), and drug-eluting bead TACE (DEB-TACE). A detailed summary of the published data is presented in supplementary table 3 (available at <http://www.karger.com/ProdukteDB/produkte.asp?doi=453010>), and the results of meta-analyses are presented in the chapter on TARE.
- TACE in comparison or combined with other therapies: In different studies, TACE was compared or combined with other therapies/controls: TACE versus surgical resection, TACE in combination with surgical resection (adjuvant TACE), TACE versus systemic chemotherapy, TACE in combination with systemic chemotherapy, TACE versus other transarterial therapies as well as TACE versus best supportive care (BSC) or no therapy. A detailed summary of the published data is presented in supplementary table 3, and the results of meta-analyses are presented in the following chapter on TARE.

Transarterial Radioembolization

- A summary of the published data is presented in supplementary table 4 (available at <http://www.karger.com/ProdukteDB/produkte.asp?doi=453010>). Recently, at least two systemic meta-analyses were published on TARE for ICC [40, 43]. In the first article, clinical outcomes and complications were assessed for different transarterial therapies including TACE, transarterial chemoperfusion (TACP), and TARE [43]. After analysis of 22 original studies (929 patients) including TARE, cTACE, DSM-TACE, and TACP, Yang et al. [43] reported pooled data for all therapies, i.e. overall and mild-to-moderate 30-day toxicity rates of 34.9 and 22.4%, a 30-day mortality rate of 0.6%, complete and partial response rates of 10 and 22.2%, a median overall survival of 12.4 months, and a 1-year overall survival rate of 53.0%. Multiple and/or infiltrating tumors as well as worse Eastern Cooperative Oncology Group (ECOG) performance status was a negative predictor for increased overall survival in some original TARE studies [57–59]. In comparison, tumor hypovascularity was a negative predictor only for DSM-TACE and TACP [46, 60]. In the second article, different transarterial therapies were compared systematically [40]. For a total of 657 patients (20 original studies), the grade III/IV toxicity (events per patient) was highest for HAI (0.35) versus cTACE (0.26) versus DEB-TACE (0.32), the response rate (complete and partial) was highest for HAI (56.9%) versus TARE (27.9%) versus cTACE (17.3%), and the overall survival (median) was highest for HAI (22.8 months) versus TARE (13.9 months) versus cTACE (12.4 months) versus DEB-TACE (12.3 months). Although the patient and tumor characteristics were markedly different in the four therapy groups – e.g. higher rate of extrahepatic disease for cTACE (48.0%) versus HAI (36.1%) and ECOG performance status 1, 2, and 3 for TARE (57.4%) and cTACE (42.0%) versus HAI (24%) –, the authors concluded that HAI results in the best tumor response, except that the survival after HAI may be limited by toxicity.
- Prospective series: A total of six prospective original series with TARE for CC were identified [59, 61–65]. All the studies included patients with advanced tumor stages and/or after failure

of first-, second-, and/or third-line therapies as suggested by the extrahepatic disease rate (31.0–76.5%), prior chemotherapy rate (29.0–100%), and prior liver-directed therapy rate (21.0–56.0%). The objective response rates after TARE range markedly between the different studies but also in one and the same study since different classification systems (RECIST, PET Response Criteria In Solid Tumors (PERCIST), and/or European Association for the Study of the Liver (EASL) criteria) were used and compared. Accordingly, Ibrahim et al. [64] reported objective response rates of 27.0% for RECIST but 77.0% for EASL. Similarly, Camacho et al. [61] published response rates of 0% for RECIST and 77.7% for PERCIST. For the cited original TARE studies, the overall survival from diagnosis and from TARE was 20.4–25.1 and 9.3–16.3 months, respectively [59, 61, 65]. Four of the six cited studies – all of them with grade II level of evidence (according to the National Health and Medical Research evidence hierarchy) – were included in a review article with a specific analysis of toxicity [43, 59, 63–65]. The acuity of toxicity was published in two studies, with <30 days and 2 days being listed [59, 63]. Only one original study reported on the overall toxicity rate (89.0%) [65]. Data on the severity of toxicity were indicated in all four studies, with a grade III/IV toxicity rate (according to WHO toxicity grades) ranging from 0 to 11% [63, 65]. The grade I/II toxicity rate, however, was published in only one of the four studies and amounted to 79% [59].

Discussion

Regarding the multiple available locoregional therapies for ICC, there is a lack of prospective randomized controlled trials. Controlled case series (unfiltered data) were identified for RFA and MWA (vs. surgical resection) as well as for TACE (vs. surgical resection, systemic chemotherapy, BSC, and/or no therapy). Additionally, overview and review articles including systematic meta-analyses (filtered information) were identified for RFA (including patients with primary and/or recurrent ICC) and different transarterial therapies such as HAI, TACE, and TARE (including patients with liver-only and liver-dominant extrahepatic metastatic disease). Critical analysis of those articles, however, resulted in the detection of at least in parts striking discrepancies between the data presented in the overview and review articles and in the original publication. On the basis of the very promising original data published for liver-targeted therapies, prospective randomized controlled trials can overcome study bias such as heterogeneous patient and tumor characteristics and inconsistent therapeutic regimens. After a review of the literature, four aspects are worthy of discussion in the context of locoregional therapy and CC: (i) Is the

oncologic outcome after RFA and TACE comparable with surgical resection in selected patients?; (ii) adjuvant TACE might offer an advantage in the adjuvant setting in patients with high risk for early intrahepatic recurrence and should be evaluated in trials; (iii) RFA, MWA, and different transarterial therapies are safe and highly effective for both recurrent ICC after potentially curative surgical resection or thermal ablation and for conversion to resectability (neoadjuvant locoregional therapy); and (iv) chemotherapy-based transarterial therapies show a survival benefit and improve the quality of life in patients with liver-only and liver-dominant extrahepatic metastatic disease when compared with systemic chemotherapy, BSC, and/or no therapy; however, data from prospective trials is lacking. With a focus on technical issues, for thermal ablation, homogeneous ablation zones (considering the desmoplastic growth pattern of ICC) and homogeneous safety margins of at least 1 cm (due to the ill-defined margins of ICC on computed tomography/magnetic resonance imaging/ultrasound) and for different transarterial therapies, optimization of the protocols (e.g. doses and types of chemotherapeutic agents, types and sizes of embolic agents, internal radiation dose, treatment intervals, and response evaluation) are of particular relevance [3, 4, 6, 18]. For the future, complex multimodal concepts are the key to further improve progression-free and overall survival as well as the quality of life in patients with CC in different stages. For example, Andrasina et al. [44] presented an interdisciplinary approach for symptomatic irresectable ICC and ECC by means of biliary stent implantation, brachytherapy, and chemotherapy. After successful biliary drainage (metallic stent placement and intraluminal brachytherapy), patients were assigned either to an arm with transarterial chemotherapy (for patients with hypervascular tumors) or to an arm with intravenous chemotherapy (for patients with hypovascular tumors). A total of 17 patients received transarterial chemotherapy, either as HAI or TACE. Intravenous chemotherapy was performed in 23 patients. For transarterial chemotherapy and intravenous chemotherapy, the median overall survival was 25.2 and 11.5 months, respectively, and the 1-, 2-, and 3-year overall survival rates were 88.2 and 43.5%, 52.9 and 25.4%, and 10.1 and 0%, respectively ($p < 0.05$ for the overall survival). Multiple other publications present concepts combining established and advanced interdisciplinary therapies such as MWA in combination with TACE or RFA in combination with systemic molecular therapies [66–70]. Such innovative concepts should be furthered continuously.

Disclosure Statement

All authors declare that there is nothing to disclose regarding this article.

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