

Review Article

Locoregional Therapies of Cholangiocarcinoma

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Table 1. RFA and MWA for Primary and Recurrent Intrahepatic Cholangiocarcinoma (ICC)

Authors / year	Patients (n) / tumors (n) / primary ICC (%) / recurrent ICC (%) / tumor diameter (cm)	Extrahepatic metastatic disease ¹ (%) / prior therapy (%) / reason for surgical infeasibility	RFA (%) / MWA (%) / technique / total number of treatment sessions	Control group	Complete tumor necrosis ^{2,3} (%) / local tumor progression ⁴ (%) / overall treatment success ⁵ (%)	Overall survival ⁶ / median (months) / 1-year (%) / 2-year (%) / 3-year (%) / 5-year (%)	Complications ⁷ / minor (%) / major (%)
Choi et al. / 2005 [71]	10 / 10 / 100 / 0 / 3.4 ⁺	n.r. / n.r. / patient refusal, advanced age, comorbidity and/or poor hepatic reserve	100 / 0 / percutaneous US-guided / 12	n.r.	80.0 ⁺⁺⁺ , ⁺⁺⁺⁺ , ⁺⁺⁺⁺⁺ / 10.0 ⁺⁺⁺⁺ , ⁺⁺⁺⁺⁺ / 70.0 ⁺⁺⁺⁺	n.r. / n.r. / n.r. / n.r. / n.r.	33.3 ⁺⁺⁺⁺⁺ / 8.3 ⁺⁺⁺⁺⁺
Carafillo et al. / 2010 [14]	6 / 6 / 100 / 0 / 3.5 ⁺	n.r. / n.r. / advanced age, comorbidity and/or poor hepatic reserve	100 ⁺⁺⁺⁺⁺ / 0 / percutaneous US-guided / 12	n.r.	66.7 ⁺⁺⁺⁺ , [*] / 16.7 ⁺⁺⁺⁺ , ^{**} / 50.0 ⁺⁺⁺⁺	17.5 / 100 / n.r. / n.r. / n.r.	16.7 ⁺⁺⁺⁺ / 0
Kim et al. / 2011 [13]	13 / 17 / 100 /	15.4 ⁺⁺⁺⁺ / n.r. / comorbidity, poor hepatic reserve and/or	100 / 0 / percutaneous	n.r.	88.2 ⁺⁺⁺⁺⁺ , ^{****} / 30.8 ⁺⁺⁺⁺ , ^{****} / 53.8 ⁺⁺⁺⁺	38.5 / 85.0 / n.r.	n.r. ^{****} / 5.9 ⁺⁺⁺⁺⁺

	0 / 4.1 ⁺	disease	US-guided / 17			51.0 / 15.0	
Kim et al. / 2011 [18]	20 / 29 / 0 / 100 / 1.5 ⁺	0 / 100 / n.r.	100 / 0 / percutaneous US-guided / 30	n.r.	100/ 24.1 ⁺⁺⁺⁺⁺ / 75.9 ⁺⁺⁺⁺⁺ . ^{****}	27.4 28.4 (from diagnosis) / 70.0 / 60.0 / 21.0 / n.r. (4-year overall survival: 21.0)	n.r. ^{****} / 6.7 ⁺⁺⁺⁺⁺
Fu et al. / 2011 [72]	17 / 26 / 57.7 / 42.3 / 4.4 ⁺⁺	41.2 / 58.8 ⁺⁺⁺⁺ / patient refusal, comorbidity and/or poor hepatic reserve	100 ^{*****} / 0 / percutaneous (88.2%) ⁺⁺⁺⁺ open (11.8%) ⁺⁺⁺⁺ US-guided (100%) ⁺⁺⁺⁺ / 28	n.r.	100/ 17.6 ⁺⁺⁺⁺⁺ / 82.4 ⁺⁺⁺⁺⁺ . ^{****}	33.0 / 84.6 / n.r. 43.3 / 28.9	n.r. ^{****} / 3.6 ⁺⁺⁺⁺⁺
Fu et al. / 2011 [17]	12 / 19 / 0 / 100 / 3.2 ⁺⁺	100 / 100 / n.r.	100 ^{*****} / 0 / percutaneous (83.3%) ⁺⁺⁺⁺ open (16.7%) ⁺⁺⁺⁺ US-guided (100%) ⁺⁺⁺⁺ / 19	n.r.	100/ 10.5 ^{*****} / 89.5 ^{*****}	30.0 / 87.5 / n.r. / 37.5 / n.r.	n.r. ^{****} / 5.3 ⁺⁺⁺⁺⁺
Giorgio et al. / 2011	10 / 12 / 75.0 /	0 / 10 / patient refusal, poor	100/ 0 / percutaneous	n.r.	66.7 ^{*****} / 8.3 ^{*****} / 58.3 ^{*****} .	19.5 (subgroup with primary ICC only) 19.5 (entire	30.0 ⁺⁺⁺⁺⁺ / 0

[15]	25.0 ^{*****} / 3.7 ⁺	hepatic reserve and/or tumor size	US-guided / 16			collective) / 100 (entire collective) 100 (subgroup with primary ICC only) / n.r. / 83.3 (entire collective) 80.0 (subgroup with primary ICC only) / 83.3 (entire collective) n.r. (subgroup with primary ICC only)	
Yu et al. / 2011 [19]	15 / 24 / 100 / 0 / 3.2 ⁺	n.r. / 20.0 / advanced age, comorbidity and/or tumor size and location	0 / 100 / percutaneous US-guided / 38	n.r.	91.7 ^{*****} / 25.0 ^{*****} / 66.7 ^{*****}	10.0 / 60.0 / 60.0 / n.r. / n.r.	93.3 (pain) ⁺⁺⁺⁺ 80.0 (fever) ⁺⁺⁺⁺ 100 (elevated transaminase levels) ⁺⁺⁺⁺ 6.7 (subcapsular hematoma) ⁺⁺⁺⁺ 53.3 (pleural effusion) ⁺⁺⁺⁺ / 7.9 ⁺⁺⁺⁺⁺
Haidu et al. / 2012 [73]	11 / 36 / 50.0 / 50.0 / 3.0 ⁺⁺	n.r. / 63.6 / comorbidity, tumor size and location and/or extrahepatic metastatic disease	100 / 0 / percutaneous CT-guided stereotactic / 23	n.r.	91.7 ^{*****} / 8.3 ^{*****} / 83.3 ^{*****}	60.0 / 91.0 / n.r. / 71.0 / n.r.	n.r. / 13.0 ⁺⁺⁺⁺⁺
Xu et al. / 2012	18 /	0 /	76.0 /	n.r.	92.0 ^{*****} /	8.8 / 36.3 (entire	11.1 ⁺⁺⁺⁺⁺ /

[20]	25 / 32.0 / 68.0 / 2.5 ⁺	100 / patient refusal	24.0 / percutaneous US-guided / 25		n.r. **** / n.r. ****	collective) 75.0 (subgroup with primary ICC) / n.r. / 30.3 (entire collective) 62.5 (subgroup with primary ICC) / 30.3 (entire collective) 62.5 (subgroup with primary ICC)	0
Zhang et al. / 2013 [21]	77 versus 32 / n.r. **** / 0 versus 0 / 100 versus 100 / n.r. ****	0 versus 0 / 45.5 versus 50.0 / comorbidity and/or tumor size and location	n.r. / n.r. / percutaneous US-guided / n.r.	RFA/MWA versus surgical resection	n.r. **** / n.r. **** / n.r. ****	21.3 versus 20.3 / 69.8 versus 83.8 **** / 37.3 versus 38.0 **** / 20.5 versus 17.1 **** / n.r.	n.r. **** / n.r. ****
Bale et al. / 2013 [74]	17 / 52 / n.r. / n.r. /	n.r. / n.r. / n.r.	100 / 0 / percutaneous CT-guided	n.r.	n.r. / 11.5 / n.r.	60.0 / n.r. / n.r. / n.r. /	n.r. **** / n.r. ****

	2.1 ⁺		stereotactic / n.r.			68.0	
Butros et al. / 2014 [16]	7 / 9 / 11.1 / 88.9 / 2.4 ⁺⁺	0 / 89.9 / n.r.	100 / 0 / percutaneous CT-guided or CT-guided and US-guided / n.r.	n.r.	100 / 11.1 / 89.1	38.5 / 100 / n.r. / 60.0 / 20.0	0 / 0
Yang et al. / 2015 [70]	26 / 39 / 76.9 ⁺⁺⁺⁺ / 23.1 ⁺⁺⁺⁺ / 3.6 ⁺⁺	0 / 23.1 / tumor size and/or location	0 / 100 ^{*****} / percutaneous US-guided / n.r.	n.r.	92.3 ^{*****} / 30.8 ⁺⁺⁺⁺ / n.r.	19.5 / 69.2 / 61.5 / n.r. / n.r.	88.5 (fever) ⁺⁺⁺⁺ 84.6 (pain) ⁺⁺⁺⁺ 11.5 (thrombocytopenia) ⁺⁺⁺⁺ 7.7 (pleural effusion) ⁺⁺⁺⁺ 3.8 (vomiting) ⁺⁺⁺⁺ / 0

extrapolated from the given data (in some cases, due to at least partially imprecise data presentation in the original study, double calculations cannot be precluded); ²defined as complete absence of viable tumor in the ablation zone detected in the first follow-up imaging after treatment [75]; ³after one (primary) or multiple (secondary) treatment sessions; ⁴defined as viable tumor in the ablation zone detected after an unremarkable first follow-up imaging after treatment [75]; ⁵defined as complete absence of viable tumor in the ablation zone during the entire follow-up [75]; ⁶from treatment; ⁶according to Clavien-Dindo or SIR classification of complications [76]; n.r. ⁺mean; ⁺⁺median; ⁺⁺⁺complete necrosis in 100% of tumors ≤3.0 cm as well as in 75% of tumors >3.0 cm and ≤5.0 cm; ⁺⁺⁺⁺incomplete necrosis only in larger tumors (4.6 cm and 6.8 cm); ⁺⁺⁺⁺on number of patient basis; ⁺⁺⁺⁺16 months after initial treatment; ⁺⁺⁺⁺on number of treatment basis; ⁺⁺⁺⁺blatant TAE was performed before RFA in two patients with larger tumors (5.0 cm and 5.8 cm); ^{*}incomplete necrosis only in larger tumors (5.0 cm and 5.8 cm); ^{**}12 months after initial treatment; ^{***}incomplete necrosis only in larger tumors (7.0 cm and 8.0 cm); ^{****}7 months, 31.0 months, 32.2 months and 34.8 months after initial treatment; ^{*****}or reported non-specifically in different patients; ^{*****}adjuvant therapies in 41.2% of patients; ^{*****}on number of tumor basis; ^{*****}there was only one patient without primary ICC, however with three recurrent ICCs; ^{''}overall treatment success of 100% in tumors ≤3.4 cm; ^{'''}overall treatment; ^{''''}all prior therapies consisted of preventive TACE; ^{''''''}for patients with tumors ≤3.0 cm, the survival was comparable between RFA/MWA and surgical resection (0.362), however for patients with tumors >3.0 cm, the survival was significantly better for surgical resection compared with RFA/MWA (p=0.037); ^{''''''''}RFA/MWA as salvage was performed in 42.9% of ineffective treatments; ^{''''''''''}RFA/MWA as salvage was performed in 100% of ineffective treatments; ^{''''''''''''}all MWA procedures performed in combination with TACE; n.r. - not reported; note: the specific RFA/MWA technique can be obtained from the original studies

Table 2. HAI for Unresectable Cholangiocarcinoma (CC)

Authors / year	Patients (n) / ICC (%)	Extrahepatic metastatic disease (%) ¹ / prior therapy (%)	HAI specifications implantation technique / complications ² / chemotherapy / embolic agent / cycles / device-related technical failure ³	Control group	Objective response complete and partial response (%) / stable disease (%) / conversion to resectability	Overall survival ⁴ median (months) / 1-year (%) / 2-year (%) / 3-year (%) / 5-year (%)	Toxicity ⁵ grade I/II (%) / grade III-V (%)
Tanaka et al. / 2002 [32]	11 / 100	36.6 / n.r.	radiological / n.r. / 5-fluorouracil adriamycin epirubicin cisplatin mitomycin c ^{**} / n.r. / 51 ⁺⁺⁺⁺ / n.r.	n.r.	63.3 (WHO) / 18.2 (WHO) / n.r.	26.0 ⁺⁺⁺⁺ / 90.9 / 50.5 / 20.2 / 0 ^{*****}	n.r. ^{..} / 27.2 ^{***}
Shitara et al. / 2008 [31]	20 / 100	85.0 / 45.0	radiological / 0 (5 ⁺) / mitomycin c ^{**,+} / degradable starch microspheres	n.r.	50.0 (RECIST) / 40.0 (RECIST) (14.1 / 59.0 ^{*****} / 21.0 ^{*****} / n.r. / n.r.	Between 0 (thrombocytopenia) and 55.0 (nausea, vomiting) ^{***,++++} / 5.0 (anorexia) ^{***}

			(n.r.) ^{**} / 8 ^{**} / n.r. ⁺⁺⁺⁺				5.0 (nausea, vomiting) ^{***} 15.0 (gastroduodenal ulcer) ^{***} 10.0 (epigastralgia) ^{**} *
Mambrini et al. / 2007 [26]	20 / 60.0	15.0 / 30.0 (entire collective)	radiological / 0 / epicubicin ^{*.#####} / cisplatin ^{*.#####} / n.r. / 4 ^{**} / 0 ^{***}	n.r.	31.5 (WHO, entire collective) / 47.5 (WHO, entire collective) / n.r.	18.0 (entire collective) / 18.0 (subgroup with ICC) / 74.0 (entire collective) / n.r. / n.r. / n.r.	60.4 ^{*****.+++} / 8.8 ^{*****.+++}
Jarnagin et al. / 2009 [24]	34 / 76.5	0 (entire collective) / 20.6 (entire collective)	surgical / n.r. / floxuridine [°] / n.r. / 7 ^{**} / 23.5 ^{***}	n.r.	47.1 (RECIST, entire collective) / 41.2 (RECIST, entire collective) / 2.9 (entire collective) 3.8 (subgroup with ICC)	n.r. / 88.0 / 67.0 / 29.0 / n.r.	n.r. ^{**} / 14.7 (entire collective) ^{***}
Inaba et al. / 2011 [23]	25 / 100	36.0 / 48.0	radiological / 0 ^{#####} / gemcitabine ^{**} / n.r. / 5 ^{**} / 24.0 ^{***}	n.r.	12.0 (RECIST, liver) 12.0 (RECIST, whole body) / 64.0 (RECIST, liver) 60.0 (RECIST, whole body) / n.r.	11.2 / 47.0 ^{*****} / 18.0 ^{*****} / 0 ^{*****} / 0 ^{*****}	n.r. ^{**} / 20.0 (neutropenia) ^{***} , +++ 8.0 (elevated gamma-glutamyl transpeptidase)* **,+++ 4.0 (elevated aspartat

							aminotransferase) ^{***, +++} 4.0 (elevated alanin aminotransferase) ^{***, +++} 8.0 (elevated bilirubin) ^{***, +++} 4.0 (nausea) ^{***, +++} 4.0 (fatigue) ^{***, +++}
Kemmeny et al. / 2011 [25]	22 versus 34 / 81.8 versus 76.4	0 (entire collective) / versus 0 (entire collective) / 13.6 ^{*****} (entire collective) versus 14.7 ^{*****} (entire collective)	HAI plus systemic bevacizumab versus HAI only	38.8 (RECIST, subgroup with ICC) versus 57.6 (RECIST, subgroup with ICC) / 61.1 (RECIST, subgroup with ICC) versus 38.4 (RECIST, subgroup with ICC) / 13.6 (entire collective) versus n.r. (entire collective) /	31.1 (entire collective) versus 29.5 (entire collective) / 87.0 (entire collective) ^{*****} versus 92.0 (entire collective) ^{*****} / 62.0 (entire collective) ^{*****} versus 47.0 (entire collective) ^{*****} / n.r. / n.r.	n.r. / 22.7 (elevated aspartat aminotransferase) ^{***, +++} versus 0.0 (elevated aspartat aminotransferase) ^{***, +++} 22.7 (elevated bilirubin ≥ 2 mg/dl) ^{***, +++} versus 5.8 (elevated bilirubin ≥ 2 mg/dl) ^{***, +++} 27.0 (doubling of alkaline phosphatase) ^{***, +++} versus 0 (doubling of alkaline phosphatase) ^{***}	

							+++
Sinn et al. / 2013 [27]	37 / 86.4	58.0 (entire collective / 32.0 ^{*****} (entire collective)	radiological / 0 / oxaliplatin ** 5-fluorouracil** folinic acid** / n.r. / 9 (entire collective)** / 29.7 (entire collective) ^{***}	n.r.	16.2 (RECIST, entire collective) / 48.6 (RECIST, entire collective) / n.r.	13.5 (entire collective) 9.2 (subgroup with prior systemic chemotherapy) 13.6 (subgroup without prior systemic chemotherapy) 13.0 (subgroup with ICC) / 57.0 (entire collective) / 23.0 (entire collective) / 12.0 (entire collective) / n.r.	n.r. / 10.8 (leucopenia) 5.4 (thrombocytopenia) 18.9 (elevated transaminase levels) 29.7 (elevated bilirubin) 2.7 (neurotoxicity) 8.1 (abdominal pain) 2.7 (diarrhea) 2.7 (nausea) 10.8 (other)
Sinn et al. / 2013 [77]	70 / 52.9	44.3 (entire collective) 56.8 (subgroup with ICC) / n.r. ⁺⁺⁺⁺⁺	radiological / 0 / oxaliplatin ** 5-fluorouracil** folinic acid** / n.r. / 6 (entire collective)** / 5.0 (total, entire collective) ^{*****} 0.9 (HAI limiting, entire collective) ^{*****}	n.r.	n.r. / n.r.	9.0 / n.r. / n.r. / n.r. / n.r.	n.r. / 42.9 (entire collective) ^{***} 7.3 (entire collective) ^{*****}

Subbiah et al. / 2013 [28]	40 / 75.0	82.5 (entire collective) ^{****} / 100 (entire collective)	n.r. ^{#,+++} / n.r. / n.r. ^{##,###,+++} / n.r. / 2 ^{##} . ⁺⁺⁺ (entire collective) / 5.8 ^{###}	n.r. ^{##,+++}	7.5 (RECIST, entire collective) / 42.5 (RECIST, entire collective) / n.r.	4.2 (entire collective) / 21.0 ^{*****} / 6.0 ^{*****}	n.r. ^{..} / 7.5 ^{***} (entire collective)
Ghiringhelli et al. / 2014 [30]	12 / 100	0 / 100	radiological / n.r. / gemcitabine ^{**} / oxaliplatin ^{**} / n.r. / 7 ^{**} / 16.7 ^{****}	n.r.	66.6 (RECIST) / 25.0 (RECIST) / 16.7	20.3 25.1 ^{*****} / 92.0 ^{*****} / 46.0 ^{*****} / 46.0 ^{*****} 23.0 ^{*****}	n.r. ^{..} / 14.9 ^{*****}
Massani et al. / 2015 [22]	11 / 100	0 / 0	surgical / 0 / folinic acid [*] / oxaliplatin [*] / 5-fluorouracil [*] / n.r. / 8 ^{**} / 0 ^{***}	n.r.	45.5 (mRECIST) / 18.2 (mRECIST) / 27.3	17.6 (entire collective) 15.3 (subgroup with HAI only) 23.6 (subgroup with conversion to resectability) / n.r. / n.r. / n.r. / n.r.	n.r. ^{..} / 36.6 ^{***}

¹extrapolated from the given data (in some cases, due to at least partially imprecise data presentation in the original study, double calculations cannot be precluded); ²peri-operative/peri-interventional; ³during the course of HAI; ⁴from treatment; ⁵CTCAE/WHO toxicity grades; *according to a specific regimen; **median; ***on number of patient basis; ****one case with irreversible catheter occlusion and one case with the need of transarterial embolization of extrahepatic arteries since a duodenal ulcer developed during HAI; *****on number of cycle basis; *****from the time of diagnosis; *****extrapolated from the presented overall survival distribution; *****at least; +no implantation of the port catheter possible since severe stenosis of the hepatic artery; ++14 patients received salvage chemotherapy performed as HAI with 5-fluorouracil and five patients received salvage chemotherapy performed as systemic chemotherapy with gemcitabine; +++further details can be obtained from the original study; ++++mean; +++++in case of epigastralgia during/after a cycle, angiography and re-embolization of the right

gastric artery or dose adjustment was performed; ⁺⁺⁺⁺⁺a total of 51 prior therapies were performed in the entire collective (and 21 prior therapies were performed in the subgroup with ICC); [#]42.5% of all patients received HAI; ^{##}the entire collective received a range of different and complex therapies; ^{###}also in combination with systemic chemotherapy; ^{####}one patient with HAI developed an arteriovenous fistula; ^{#####}extrahepatic findings of uncertain dignity; ^{#####}in combination with oral systemic chemotherapy (capecitabine); ^{#####}according to inclusion criteria; HAI plus systemic bevacizumab was stopped prematurely due to increased toxicity; ^{''}or reported non-specific in different patients; n.r. - not reported; note: the specific doses for the different HAI regimens can be obtained from the original studies and/or from the main body

Table 3. TACE for Intrahepatic Cholangiocarcinoma (ICC)

Authors / year	Patients (n)	Extrahepatic metastatic disease (%) ¹ / prior therapy (%)	TACE technique type / chemotherapy / embolic agent	Control group	Objective response complete and partial response (%) / stable disease (%) / conversion to resectability	Overall survival ² median (months) / 1-year (%) / 2-year (%) / 3-year (%) / 5-year (%)	Toxicity ³ grade I/II (%) / grade III-V (%)
Burger et al. / 2005 [48]	17	17.6 / 35.3	cTACE / cisplatin doxorubicin mitomycin c / iodized oil microparticles (polyvinyl alcohol, diameter of 150- 250 µm) microspheres (tris- acryl, diameter of 300-500 µm)	n.r.	78.6 (RECIST)/ n.r. / 11.8	23.0 / 77.0** / 30.0** / n.r. / n.r.	29.4*****/ 11.7*****
Kirchhoff et al. / 2005 [78]	8	n.r. / n.r.	DSM-TACE (plus systemic chemotherapy) / doxorubicin cisplatin / microspheres (degradable starch microspheres, diameter of ≈45 µm, biodegradation	n.r.	37.5 (WHO) / 62.5 (WHO) / 12.5	12.0 / n.r. / n.r. / n.r.	75.7 / 0

			half-time of ≈20 min)				
Herber et al. / 2007 [55]	15	0 / 46.7	cTACE / mitomycin C / iodized oil (in mixture with mitomycin C)	n.r.	6.7 (RECIST) / 60.0 (RECIST) ^{****} / n.r.	21.1 ⁺⁺ / 54.5 / 27.5 / 27.5 / n.r.	40.0 / 6.7
Kim et al. / 2008 [45]	49 ^{*****}	51.0 ^{*****} / n.r.	cTACE (TACP ⁺) / cisplatin / iodized oil (in mixture with cisplatin) / hand-cut gelatin sponge (diameter of ≈1 mm)	n.r.	20.4 (RECIST) ^{*****} / 30.6 (RECIST) ^{*****} / n.r.	12.0 ^{*****} / 46.0 ^{*****} / 38.0 ^{*****} / 30.0 ^{*****} / n.r.	n.r. / n.r.
Aliberti et al. / 2008 [44]	11 versus 9	n.r. / 100 vs. 100	DEB-TACE / doxorubicin / microspheres (polyvinyl alcohol, diameter of 100-300 and/or 300-500 μm)	TACE vs. systemic chemotherapy	100 (RECIST) ⁺⁺⁺⁺⁺ vs. n.r. / 0 (RECIST) ⁺⁺⁺⁺⁺ vs. n.r. / n.r.	13.0 vs. 8.0 / 77.0 ^{**} vs. 34.0 ^{**} / n.r. / n.r.	100 ⁺⁺⁺⁺ vs. n.r. / 0 ⁺⁺⁺⁺ vs. n.r.
Gusani et al. / 2008 [49]	42	45.2 / n.r.	cTACE / gemcitabine / oxaliplatin / cisplatin / microspheres (tris-acryl)	n.r. ^{*****}	0 (RECIST) ^{*****} / 57.1 (RECIST) ^{*****} / n.r.	9.1 (all cTACE regimens) / 6.3 (cTACE with gemcitabine only) vs. 18.8 (cTACE with gemcitabine)	38.1 ^{*****} / 16.7 ^{*****}

						followed by cisplatin) vs. 13.0 (cTACE with gemcitabine followed by oxaliplatin) vs. 13.8 (cTACE with gemcitabine in combination with cisplatin) vs. 12.5 (cTACE with gemcitabine in combination with cisplatin followed by oxaliplatin) / n.r. / n.r. / n.r. / n.r.	
Harder et al. / 2009 [79]	13	0 / 69.2	DEB-TACE / irinotecan / microspheres (n.r.)	n.r.	7.7 (RECIST) / 61.5 (RECIST) / n.r.	n.r. / n.r. / n.r. / n.r.	46.2 / 30.8
Poggi et al. / 2009 [47]	9 vs. 11	11.1 vs. 18.2 / 100 vs.	DEB-TACE (plus systemic chemotherapy (gemcitabine and oxaliplatin))/ oxaliplatin / microspheres	TACE vs. systemic chemotherapy	44.4 vs. n.r. ⁺⁺⁺⁺ / 55.6 vs.	30.0 vs. 12.7 / 76.0** vs.	15.1 ⁺⁺⁺⁺⁺ vs. 25.4 ⁺⁺⁺⁺⁺ / 1.4 ⁺⁺⁺⁺⁺ vs.

		n.r.	(sodium acrylate alcohol co-polymer, diameter of 50-100 µm)		n.r. ⁺⁺⁺⁺ / 33.3 vs. 0	48.0** / 57.0** vs. 0** / 38.0** vs. 0** / n.r.	6.3 ⁺⁺⁺⁺⁺
Park et al. / 2010 [50]	72 vs. 83	54.2 vs. 60.2 / n.r.	cTACE / cisplatin / iodized oil (in mixture with cisplatin) hand-cut gelatin sponge (diameter of ≈1 mm)	TACE vs. BSC	22.7 (RECIST) vs. n.r. / 66.7 (RECIST) vs. n.r. / n.r.	10.7 vs. 3.9 / 46.9 vs. 21.9 / 18.8 vs. 3.1 / n.r. / n.r.	n.r. / 36.1 ^{*****} vs. n.r.
Kiefer et al. / 2010 [53]	62 [#]	22.6 / 30.6	cTACE (plus systemic chemotherapy ⁺⁺⁺⁺⁺ / mitomycin c doxorubicin cisplatin / iodized oil (in mixture with different chemotherapeutic	n.r.	11.1 (entire collective) ^{##} / 64.4 (entire collective) ^{##}	20.0 (entire collective, from diagnosis) 15.0 (entire collective, from treatment) 28.0 (subgroup undergoing TACE plus systemic chemotherapy) 16.0 (subgroup undergoing TACE	65.0 ⁺⁺⁺⁺ / 8.1 ^{*****}

			agents) microparticles (polyvinyl alcohol, diameter of 150- 250)			only) / 75.0 (entire collective, from diagnosis) 61.0 (entire collective, from treatment) / 39.0 (entire collective, from diagnosis) 27.0 (entire collective, from treatment) / 17.0 (entire collective, from diagnosis) 8.0 (entire collective, from treatment) / n.r.	
Andrasina et al. / 2010 [65]	17 vs. 23	0 / n.r.	cTACE (HAI ^{#####}) ^{#####} / Cisplatin 5-fluorouracil leucovorin / iodized oil	TACE versus systemic chemotherapy	n.r. / n.r. / n.r.	25.2 vs. 11.5 / 88.2 vs. 43.5 / 52.9 vs. 25.4 / 10.1 vs. 0 /	n.r. / n.r.

						n.r.	
Chaiteeraki j t al. / 2010 [80]	32 vs. n.r.	n.r. / n.r.	n.r. / n.r. / n.r.	TACE vs. no treatment	20.5 (mRECIST) vs. n.r. / 71.1 (mRECIST) vs. n.r. / n.r.	10.7 vs. 3.9 / 46.9 vs. 21.9 / 18.8 vs. 3.1 / n.r. / n.r.	n.r. / n.r.
Schiffman et al. / 2011 [54]	24	83.3 / 41.7	DEB-TACE (plus systemic chemotherapy ^{###}) / doxorubicin irinotecan / microspheres (polyvinyl alcohol, diameter of 100- 300,300-500 and/or 500-700 µm)	n.r.	8.3 (RECIST) ^{###} 79.2 (mRECIST) ^{###} / 83.3 (RECIST) ^{###} 12.5 (mRECIST) ^{###} / 12.5	13.6 (entire collective) 17.5 (TACE plus systemic chemotherapy) / 67.0** (entire collective) / 37.0** (entire collective) / 37.0** (entire collective) / n.r.	16.7 ^{####} / 9.5 ^{####}
Shen et al. / 2011 [81]	53 vs. 72	5.7 vs. 9.7 / n.r.	cTACE / 5-fluorouracil carboplatin epirubicin hydroxycamptothec in (irinotecan)	TACE plus surgical resection vs. surgical resection only	n.r. / n.r.	n.r. (TACE plus surgical resection, entire collective) vs. n.r. (surgical resection only, entire collective) 12.0 (TACE plus	n.r. / n.r.

			<p>gemcitabine / iodized oil (in mixture with different chemotherapeutic agents)</p>			<p>surgical resection, subgroup with recurrence ≤ 3 months) vs. 5.0 (surgical resection only, subgroup with recurrence ≤ 3 months) 32.0 (TACE plus surgical resection, subgroup with recurrence > 3 months) vs. 26.0 (surgical resection only, subgroup with recurrence > 3 months) / 69.8 (TACE plus surgical resection, entire collective) vs. 54.2 (surgical resection only, entire collective) 48.2 (TACE plus surgical resection, subgroup with recurrence ≤ 3 months) vs. 7.4 (surgical resection only, subgroup with recurrence ≤ 3</p>	
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						<p>months)</p> <p>92.3 (TACE plus surgical resection, subgroup with recurrence >3 months)</p> <p>vs.</p> <p>82.2 (surgical resection only, subgroup with recurrence >3 months) /</p> <p>n.r. /</p> <p>37.7 (TACE plus surgical resection, entire collective)</p> <p>vs.</p> <p>25.0 (surgical resection only, entire collective)</p> <p>25.9 (TACE plus surgical resection, subgroup with recurrence ≤3 months)</p> <p>vs.</p> <p>0 (surgical resection only, subgroup with recurrence ≤3 months)</p> <p>50.5 (TACE plus surgical resection, subgroup with recurrence >3 months)</p> <p>vs.</p> <p>40.4 (surgical</p>	
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						<p>resection only, subgroup with recurrence >3 months) /</p> <p>28.3 (TACE plus surgical resection, entire collective)</p> <p>vs.</p> <p>20.8 (surgical resection only, entire collective)</p> <p>14.8 (TACE plus surgical resection, subgroup with recurrence ≤3 months)</p> <p>vs.</p> <p>0 (surgical resection only, subgroup with recurrence ≤3 months)</p> <p>42.3 (TACE plus surgical resection, subgroup with recurrence >3 months)</p> <p>vs.</p> <p>33.3 (surgical resection only, subgroup with recurrence >3 months)</p>	
Knüppel et al. / 2011 [82]	14 vs. 81	n.r. / n.r.	cTACE / n.r. / n.r.	TACE plus systemic chemotherapy vs. systemic	n.r. / n.r. / n.r.	22.0 (cTACE plus systemic chemotherapy) vs. 12.2 (systemic	n.r. / n.r.

				chemotherapy only		chemotherapy only) / 85.0 (cTACE plus systemic chemotherapy) vs. 50.0 (systemic chemotherapy only) / 41.0 (cTACE plus systemic chemotherapy) vs. 15.0 (systemic chemotherapy only) / n.r. / n.r.	
Vogl et al. / 2012 [52]	115	0 / n.r.	DSM-TACE / gemcitabine mitomycin C cisplatin / microspheres (degradable starch microspheres, diameter of ≈50 µm, biodegradation half-time of ≈60 min)	n.r.****	8.7 (RECIST) / 57.4 (RECIST) / n.r.	13.0 / 52.0 / 29.0 / 10.0 / n.r.	13.0 / 0
Kuhlmann et al. / 2012 [46]	26 vs. 10 vs.	42.3 vs. 40.0 vs.	DEB-TACE / irinotecan / microspheres (n.r.)	DEB-TACE vs. cTACE vs. systemic	3.8 (RECIST) (DEB-TACE) vs. 10.0 (RECIST) (cTACE) vs. 25.8 (RECIST) (systemic	11.7 (DEB-TACE) vs. 5.7 (cTACE) vs.	76.9 (DEB-TACE) vs. 90.0 (cTACE) vs.

	31	90.3 / 42.3 vs. 30.0 vs. 45.2		chemotherapy	chemoterhapy) / 42.3 (RECIST) (DEB-TACE) vs. 10.0 (RECIST) (cTACE) vs. 45.2 (RECIST) (systemic chemotherapy) / 3.8 (DEB-TACE) vs. n.r. (cTACE) vs. n.r. (systemic chemotherapy)	11.0 (systemic chemotherapy) / n.r. / n.r. / n.r. / n.r.	n.r. (systemic chemotherapy) / 42.3 (DEB-TACE) vs. 30.0 (cTACE) vs. 74.2 (systemic chemotherapy)
Halappa et al. / 2012 [83]	29	3.4 / 24.1	cTACE / cisplatin doxorubicin mitomycin C / iodized oil (in mixture with mitomycin C) microparticles (polyvinyl alcohol, diameter of 150-250) microspheres (tris-acryl, diameter of 350-510 µm)	n.r.	n.r. / n.r. / n.r.	19.0 months (for patients with an increase of $\geq 45\%$ in ADC in the tumor volume) 8.0 months (for patients with an increase of $\leq 45\%$ in ADC in the tumor volume) 42.0 months (for patients with an increase of $\geq 60\%$ in ADC in the tumor volume) 17.0 months (for patients with an increase of $< 60\%$ in ADC in the tumor volume) / n.r. / n.r. /	n.r. / n.r.

						n.r. / n.r.	
Wu et al. / 2012 [84]	114	n.r. / 9.6	cTACE / 5-fluorouracil carboplatin epirubicin hydroxycamptothecin (irinotecan) / iodized oil (in mixture with different chemotherapeutic agents)	TACE plus surgical resection	n.r. / n.r. / n.r.	15.3 (entire collective) n.r. (TACE plus surgical resection) vs. n.r. (surgical resection only) n.r. (TACE plus surgical resection in patients without poor prognosis factors*) vs. n.r. (TACE plus surgical resection in patients without poor prognosis factors*) / 63.0 (entire collective) 73.0 (TACE plus surgical resection) vs. 68.0 (surgical resection only) 71.0 (TACE plus surgical resection in patients with poor prognosis factors*) vs. 41.0 (TACE plus surgical resection in patients without	n.r. / n.r.

						<p>poor prognosis factors[^] /</p> <p>n.r. /</p> <p>26.0 (entire collective)</p> <p>41.0 (TACE plus surgical resection)</p> <p>vs.</p> <p>32.0 (surgical resection only)</p> <p>34.0 (TACE plus surgical resection in patients with poor prognosis factors[*])</p> <p>vs.</p> <p>0 (TACE plus surgical resection in patients without poor prognosis factors[*]) /</p> <p>15.0 (entire collective)</p> <p>27.0 (TACE plus surgical resection)</p> <p>vs.</p> <p>21.0 (surgical resection only)</p> <p>14.0 (TACE plus surgical resection in patients without poor prognosis factors[*])</p> <p>vs.</p> <p>0 (TACE plus surgical resection</p>
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						in patients without poor prognosis factors*)	
Scheuermann et al. / 2013 [51]	32 vs. 130 vs. 111	n.r. / n.r.	DEB-TACE cTACE / irinotecan mitomycin C / microspheres (n.r.) iodized oil	TACE vs. surgical resection vs. systemic chemotherapy (or BSC)	n.r. / n.r. / n.r.	11.0 vs. 28.0 vs. n.r. / 42.0 vs. 68.0 vs. 50.0** (with prior surgical exploration) 17.0** (without prior surgical exploration) / n.r. / 15.0 vs. 40.0 vs. 0** / 9.0 vs. 23.0 vs. 0**	n.r. / n.r.
Hyder et al.	128	19.7**** /	cTACE /	cTACE	25.5**** (mRECIST)	13.2 (entire	35.4**** /

/	vs.	37.4 ^{*****}	gemcitabine	vs.	34.6 ^{*****} (EASL) /	cohort)	8.1 ^{*****}
2013	13		cisplatin		61.5 ^{*****} (mRECIST)	13.4 (cTACE)	
[85]	vs.		doxorubicin	vs.	47.5 ^{*****} (EASL) /	vs.	
	11		mitomycin c		n.r.	14.3 (bland TAE)	
	vs.		other (n.r.) /	vs.		vs.	
	46		n.r.		TARE	10.5 (DEB-TACE)	
						vs.	
						11.3 (TARE) /	
						54.0 (entire cohort)	
						58.0 ^{**} (cTACE)	
						vs.	
						77.0 ^{**} (bland TAE)	
						vs.	
						32.0 ^{**} (DEB-TACE)	
						vs.	
						55.0 ^{**} (TARE) /	
						n.r. /	
						22.2 (entire cohort)	
						26.0 ^{**} (cTACE)	
						vs.	
						0 ^{**} (bland TAE)	
						vs.	
						n.r. ^{**} (DEB-TACE)	
						vs.	

						20.0** (TARE) / 16.2 (entire cohort) 20.0** (cTACE) vs. 0** (bland TAE) vs. n.r.** (DEB-TACE) vs. n.r.** (TARE)	
Li et al. / 2015 [86]	122 vs. 431	10.7 vs. 21.1 / n.r.	n.r. / n.r. / n.r.	TACE plus surgical resection vs. surgical resection only	n.r. / n.r. / n.r.	27.6 (TACE plus surgical resection, entire collective after 1:1 matching) vs. 23.2 (surgical resection only, entire collective after 1:1 matching) / 79.5 (TACE plus surgical resection, entire collective after 1:1 matching) vs. 66.4 (surgical resection only, entire collective after 1:1 matching) 61.3 (TACE plus surgical resection, subgroup with a	n.r. / n.r.

						<p>prognostic ICC survival nomogram scores ≥ 77)</p> <p>vs.</p> <p>33.8 (surgical resection only, subgroup with a prognostic ICC survival nomogram scores ≥ 77) /</p> <p>n.r. /</p> <p>47.3 (TACE plus surgical resection, entire collective after 1:1 matching)</p> <p>vs.</p> <p>41.1 (surgical resection only, entire collective after 1:1 matching)</p> <p>28.0 (TACE plus surgical resection, subgroup with a prognostic ICC survival nomogram scores ≥ 77)</p> <p>vs.</p> <p>7.0 (surgical resection only, subgroup with a prognostic ICC survival nomogram scores ≥ 77) /</p> <p>38.4 (TACE plus</p>
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						<p>surgical resection, entire collective after 1:1 matching)</p> <p>vs.</p> <p>36.0 (surgical resection only, entire collective after 1:1 matching)</p> <p>21.3 (TACE plus surgical resection, subgroup with a prognostic ICC survival nomogram scores ≥ 77)</p> <p>vs.</p> <p>6.2 (surgical resection only, subgroup with a prognostic ICC survival nomogram scores ≥ 77)</p>	
Zhao et al. / 2015 [87]	65	49.2 / n.r.	cTACE / oxaliplatin gemcitabine / iodized oil (in mixture with oxaliplatin) microparticles (gelatin sponge, diameter of 350-510 μm)	n.r.	29.2 (RECIST) / 55.4 (RECIST) / n.r.	12.0 (entire collective) 20.1 (TACE responders) 9.2 (TACE non-responders) / n.r. / n.r. / n.r. / n.r.	35.4 / 9.2

¹extrapolated from the given data (in some cases, due to at least partially imprecise data presentation in the original study, double calculations cannot be precluded); ²from treatment; ³CTCAE/WHO toxicity grades; n.r. - not reported; *tumor diameter of ≥ 5.0 cm or TNM tumor stage of $\geq \text{III}$; ** extrapolated from the presented overall survival distribution; *** further patients underwent photodynamic therapy plus

systemic chemotherapy (11) or systemic chemotherapy only (84); **** different DSM-TACE regimens were performed, however there were no statistically significant differences between the study groups; ***** data only available for the entire collective; ***** on number of patient basis; ***** different cTACE regimens were performed, and there were statistically significant differences between the study groups; ***** 35 patients were available for objective response evaluation; + in case of hypovascular tumors (with cisplatin, bit without iodized oil and hand-cut gelatin sponge); ++ from the time of diagnosis; +++ mean; ++++ on number of TACE procedure basis; +++++ 72.7% of patients showed progressive disease; +++++ local tumor response; +++++ calculated mean for all observed adverse events; +++++ TACE plus systemic chemotherapy in 18 patients and TACE only in 44 patients; # also patients with adenocarcinoma of unknown primary (likely CC); ## 45 patients were available for objective response evaluation; ### in eight patients; #### follow-up at three months; ##### as transarterial therapy, either TACE or HAI was performed (no further specific data given in the original publication); ##### as part of a complex interdisciplinary concept; ' or reported non-specific in different patients; note: the specific doses for the different TACE regimens can be obtained from the original studies and/or from the main body

Table 4. TARE for Intrahepatic Cholangiocarcinoma (ICC)

Authors / year	Patients (n)	Extrahepatic metastatic disease (%) ¹	Prior therapy surgical resection (%) / systemic chemotherapy (%) / transarterial therapy (%)	Objective response ¹ complete and partial response (%) / stable disease (%) / conversion to resectability (%)	Overall survival ² median (months) / 1-year (%) / 2-year (%) / 3-year (%) / 5-year (%)	Toxicity ^{3,4} grade I/II (%) / grade III-IV (%)
Ibrahim et al. / 2008 [63]	24	33.3	n.r. / 29.0 / n.r.	27.0 (WHO) 86.0 (EASL) / 68.0 (WHO) / 3.8	14.9 / 50.0** / 42.0** / 30.0** / n.r. /	n.r.**** / 25.0
Saxena et al. / 2010 [58]	25	48.0	40.0 / 72.0 / 8.0	25.0 (RECIST) / 45.8 (RECIST) / n.r.	9.3 / 40.0** / 27.0** / 13.0** / n.r.	n.r.**** / 16.0
Haug et al. / 2011 [62]	26	30.8	30.8 / 65.4 / 19.2***	21.7 (RECIST) 78.2 (EASL) / 65.2 (RECIST) / n.r.	11.8 / 53.0 / 31.0 / n.r. / n.r.	n.r.**** / 7.7
Rafi et al. / 2012 [64]	19	57.9	n.r. / 100 / 21.01	10.5 (RECIST) / 68.4 (RECIST) / n.r.	11.5 / 56.0 / 10.0** /	78.9 / 10.5

					n.r. / n.r.	
Hoffmann et al. / 2012 [56]	33	24.2	36.4 / 78.8 / 9.1	36.4 (RECIST) / 51.5 (RECIST) / n.r.	22.0 / 61.0** / 41.0** / 12.0**	n.r.**** / 0
Mouli et al. / 2013 [57]	46	35.0	11.0 35.0 / n.r.	25.0 (WHO) / 73.0 (WHO) / 10.9	15.6 (peripheral) 6.1 (infiltrative) / 60.0** (peripheral) 18.0** (infiltrative) / 42.0** (peripheral) 0** (infiltrative) / 16.0** (peripheral) 0** (infiltrative) / 5.0** (peripheral) 0** (infiltrative)	n.r.**** / 17.4
Camacho et al. / 2014 [60]	21	n.r.	47.6 / 100 / n.r.	0 (RECIST) 37.5 (mRECIST) / 62.5 (RECIST) 12.5 (mRECIST) / n.r.	16.3 / 56.0** / 32.0** / 18.0** / 18.0**	n.r.**** / n.r.****
Filippi et al. / 2015 [61]	17	23.5	23.5 / 88.2 / n.r.	82.4 (PERCIST) / 17.6 (PERCIST) / n.r.	14.8* / 58.0** / n.r. / n.r. / n.r.	47.1 / 5.9

¹extrapolated from the given data (in some cases, due to at least partially imprecise data presentation in the original study, double calculations cannot be precluded); ²from treatment; ³CTCAE/WHO toxicity grades; ⁴on number of patient basis; n.r. - not reported; * mean; ** extrapolated from the presented overall survival distribution; *** unspecified locoregional treatment; the specific doses for the different TARE regimens can be obtained from the original studies; **** or reported non-specific in different patients

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