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Review Article

Trans-arterial embolisation therapies for unresectable intrahepatic cholangiocarcinoma: a systematic review

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Background: Unresectable intrahepatic cholangiocarcinoma (ICC) portends a poor prognosis despite standard systemic treatments which confer minimal survival benefits and significant adverse effects. This study aimed to assess clinical outcomes, complications and prognostic factors of TAE therapies using chemotherapeutic agents or radiation.

Methods: A literature search and article acquisition was conducted on PubMed (MEDLINE), OVID (MEDLINE) and EBSCOhost (EMBASE). Original articles published after January 2000 on trans-arterial therapies for unresectable ICC were selected using strict eligibility criteria. Radiological response, overall survival, progression-free survival, safety profile, and prognostic factors for overall survival were assessed. Quality appraisal and data tabulation were performed using pre-determined forms. Results were synthesized by narrative review and quantitative analysis.

Results: Twenty articles were included (n=929 patients). Thirty three percent of patients presented with extrahepatic metastases. After treatment, the average rate of complete and partial radiological response was 10% and 22.2%, respectively. Overall median survival time was 12.4 months with a median 30-day mortality and 1-year survival rate of 0.6% and 53%, respectively. Acute treatment toxicity (within 30 days) was reported in 34.9% of patients, of which 64.3% were mild to moderate in severity. The most common clinical toxicities were abdominal pain, nausea and vomiting, and fatigue. Multiplicity, localization and vascularity of the tumor may predict worse overall survival.

Conclusions: Trans-arterial therapies are safe and effective treatment options which should be considered routinely for unresectable ICC. Consistent and standardized methodology and data collection is required to facilitate a meta-analysis. Randomized controlled trials will be valuable in the future.

Keywords: Intrahepatic cholangiocarcinoma (ICC); unresectable; embolization; survival

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Introduction

Intrahepatic cholangiocarcinoma (ICC) is a devastating malignancy of the biliary tree which is notoriously difficult to diagnose (1). Survival remains at less than 12 months after diagnosis due to clinical latency, lack of effective non-surgical therapies and aggressive tumors (1-4). Surgical resection is the only chance of cure, but in up to 70% of cases ICC is unresectable (5-8). Systemic chemotherapy and radiotherapy as primary, adjuvant or palliative treatments have poor response rates and are limited by systemic toxicities (9-14).

Since 1980, TAE has become available for targeted treatment of both primary and secondary hepatic malignancies (15). The common modalities for TAE are bland embolization, trans-arterial chemoembolization

(TACE) or chemoinfusion (TACI), and selective internal radiation therapy (SIRT). These are performed via the hepatic artery and allow selective delivery of anti-tumor agents or radioactive microspheres. This targeted approach minimizes systemic toxicity or exposure of healthy tissue to radiation.

TACE and TACI have shown to improve median survival by 2-7 months compared to systemic therapies (16). Several observational studies on SIRT have also reported similar benefits on overall survival and tumor response rates of up to 86% (17-19). In the context of inoperability and increasing evidence of survival benefit conferred by trans-arterial approach, such therapies have become important and widely used treatment options. However, systematic evaluation of data for each treatment modality remains limited.

This study reviews the effect of trans-arterial emoblisation therapies for unresectable ICC. Primary outcomes were response and survival outcomes. Secondary outcomes were treatment complications and prognostic factors for overall survival.

Methods

The structure of this systematic review followed the PRISMA guidelines (20).

Definition of treatment modalities

TACE delivers high doses of chemotherapy directly to the cancer cells via the hepatic artery. Additionally, embolic agents are injected to reduce arterial inflow and increase bioavailability of the drugs (21). Bland embolization is another form of TACE that uses particles and/or embolic agents to block blood flow to the tumor without the use of chemotherapeutic agents. Another alternative includes the use of drug-eluting beads embedded with irinotecan (DEBTACE).

TACI is a catheter-based therapy using an arterial port in the hepatic artery. Its delivery of chemotherapeutic drugs is similar to TACE, but embolization is not used in TACE. TACI maximizes targeted drug delivery by selective vessel catheterization (5).

SIRT delivers internal radiation selectively to the tumor bed. Yttrium-90 (Y90) is impregnated in glass or resin-based microspheres (5). The type, size and number of microspheres per treatment varies (22).

Eligibility criteria

Studies considered for review had the following pre-determined inclusion criteria: (I) adult patients with primary ICC; (II) unresectable, chemorefractory or failed previous surgical resection; (III) TAE as the treatment modality; and (IV) clinical outcomes and complications assessed and reported. Resectibility is assessed using patient and disease factors including comorbidities, fitness for surgery and tumor location and size (23). A tumor is deemed unresectable if clear margins cannot be achieved by resection and there are evidence of metastases (24,25).

These studies were restricted according to the following report characteristics: (I) publication date after January 2000; (II) English language; and (III) original research. The search period was restricted to be more representative of modern post-operative outcomes.

Information sources and search strategy

On December 2013, a literature search was conducted using MeSH keyword search on PubMed (MEDLINE) for all studies which matched the eligibility criteria above (*Figure 1*). An additional manual search of OVID (MEDLINE) and EBSCOhost (EMBASE) as well as bibliographies of each included study was conducted to identify studies not covered by the initial MeSH keyword search. All identified articles were retrieved from the aforementioned databases.

Study selection

Following the search, two reviewers independently performed screening of titles and abstracts after MeSH keyword and manual searches. Studies were excluded if they did not meet eligibility criteria. Consensus for studies included for review was achieved by discussion between reviewers based on the pre-determined eligibility criteria.

Studies were classified into levels of evidence using the National Health and Medical Research Council evidence hierarchy (42).

Data items and extraction

All data items for assessment of study quality (*Table 1*) and study results (*Table 2*) were pre-determined. Data extraction was then performed by two independent reviewers using a standardised protocol. Data extracted include the

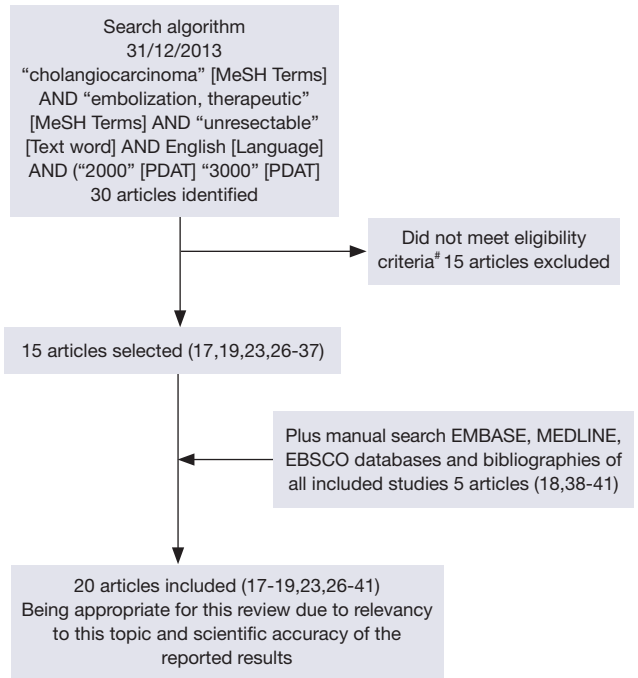

Figure 1 Search algorithm (17-19,23,26-41). #, eligibility criteria outlined in methods section: (I) adult patients with primary intrahepatic cholangiocarcinoma; (II) unresectable, chemorefractory or failed previous surgical resection; (III) patients received transarterial chemoembolization, chemoinfusion, and/or radioembolization; (IV) assessment of clinical outcomes and complications; (V) original research.

methodology, quality appraisal, patient characteristics, treatment toxicity, radiological response, overall survival, progression-free survival and prognostic factors. Overall survival and progression-free survival were determined from the time of TAE.

Synthesis of results

Data was synthesized by qualitative and quantitative review based on the outcomes criteria and data extracted in tables as outlined above. Statistical data are presented as percentages or median (range). A meta-analysis was not performed due to the following reasons: (I) heterogeneous data prevented complete meta-analysis; some studies had no reference population and others compared trans-arterial therapy with surgery or systemic chemotherapy; (II) statistical limitations due to missing data or inconsistencies in data presentation and (III) methodological inconsistencies such as varied follow-up time points for survival rates.

Risk of bias

The risk of bias in individual studies was assessed by a qualitative analysis based on study quality and data tabulated in *Table 1*.

Results

Study selection

After careful systematic selection, 20 studies were selected for review (17-19,23,26-41). Full details of the search algorithm are outlined in *Figure 1*.

Study characteristics and risk of bias within studies (Table 1)

The sample size ranged between 9 to 198. Only four studies included greater than 50 patients (30-32,38). The number of patients in most studies is low and this is a significant source of bias.

Seven studies used radioembolization (17-19,26,27,38,39). Hyder *et al.* compared TACE, DEBTACE and traditional SIRT (38). TACI was assessed in two studies (36,41). One study compared TACE with systemic chemotherapy (29) and nine studies assessed TACE with no comparators (23,28,30-33,35,37,40).

Heterogeneous patient demographics, tumor type and pathology, and treatment combinations in included studies resulted in a wide range of results derived from each article (*Tables 1,2*). This discrepancy reflects the lack of standardized protocol for trans-arterial therapies to facilitate consistent patient selection and treatment regimens. These therapies are relatively new, and although their efficacy has been reported in multiple studies, a summary of evidence is required.

Study design limited the strength of evidence of included articles. Twelve studies were retrospective (19,26,28-30,32,33,35-38,41) and no randomized controlled trial was present in this review. Both are potential sources of bias. The reasons for the lack of randomized studies may be multifactorial. In the context of known survival benefit conferred by trans-arterial therapies, it may be unethical to deny patients trans-arterial therapies.

All studies had level of evidence II and III. The results of studies were similar between lower (19,26,28-30,32,33,35-38,41) and higher level (17,18,23,27,31,34,39,40) evidence articles which demonstrates good consistency of results across studies.

Table 1 Quality appraisal

Author, year	Study design	Patients	Treatment	Follow-up duration (months)	Explicit inclusion criteria	Previous treatments (%)		Concomitant CTx	Comparison groups	Level of evidence
						CTx	Resection			
Burger (23), 2005	P	17	TACE	16	Yes	35	0	No	None	II
Herber (37), 2007	R	15	TACE	3	Yes	4	1	No	None	III
Aliberti (34), 2008	P	11	TACE + DEBTACE	NR	Yes	NR	NR	No	CTx	II
Gusani (35), 2008	R	42	TACE	NR	Yes	NR	NR	No	TACE combinations: gemcitabine only; gemcitabine followed by cisplatin; gemcitabine followed by oxaliplatin; gemcitabine + cisplatine; gemcitabine + cisplatin followed by oxaliplatin	III
[a]Ibrahim (18), 2008	P	24	Glass microspheres	17.7	Yes	29	NR	No	None	II
Kim (36), 2008	R	49	TACE, TACI	8	Yes	NR	NR	No (adjuvant radiation 33%)	TACE; TACI; TACE + TACI	III
Shitara (41), 2008	R	20	TACI	NR	Yes	0	0	No	None	III
Poggi (33), 2009	R	9	Oxaliplatin eluting microspheres-TACE	20	Yes	0	0	Yes	CTx	III
[a]Saxena (17), 2010	P	25	SIRT	8.1	Yes	18	10	Yes (28%)	No	II
[a]Haug (27), 2011	P	26	SIRT	NR	Yes	17	8	No	None	II
Kiefer (31), 2011	P	62	TACE	NR	Yes	18	7	No	None	II
Park (32), 2011	R	72	TACE	NR	Yes	NR	NR	No	Supportive treatment	III
[a]Schiffman (40), 2011	P	24	DEBTACE	13.6	Yes	80	29	No	None	II
Hoffman (19), 2012	R	33	SIRT	13.5	Yes	27	12	No	None	III

Table 1 *(continued)*

Table 1 *(continued)*

Author, year	Study design	Patients	Treatment	Follow-up duration (months)	Explicit inclusion criteria	Previous treatments (%)		Concomitant CTx	Comparison groups	Level of evidence
						CTx	Resection			
Kuhlmann (29), 2012	R	26	TACE + DEBTACE	12	Yes	5	1	No	TACE + DEBTACE; TACE; ChT	III
		10	TACE	1.8	Yes	2	0	No		
		31	ChT (gemcitabine & oxaliplatin)	13	Yes	0	7	No		
Vogl (30), 2012	R	115	TACE	NR	Yes	NR	NR	No	All TACE: mitomycin-C; gemcitabine; mitomycin-C + gemcitabine; mitomycin-C + gemcitabine +cisplatin	III
[a]Hyder (38), 2013	R	198	SIRT	NR	No	55	23	30 patients (15%)	All IAT: TACE; DEBTACE; bland embolization; Yttrium-90	III
[a]Mouli (26), 2013	R	46	SIRT	29	Yes	16	5	No	None	III
[a]Rafi (39), 2013	P	19	SIRT	15	Yes	19	NA	No	None	II
Scheuermann (28), 2013	R	32	Lipiodol and mitomycin C, doxorubicin	10	Yes	NA	NA	Adjuvant CTx	Resection; CTx/supportive	III
Median				13.5		35	11.6			
Range				1.8-29		27-100	10-40			

[a], SIRT. CTx, systemic chemotherapy; TACE, trans-arterial chemoembolization; DEBTACE, drug eluting beads TACE; NA, not applicable; NR, not reported; P, prospective; R, retrospective; TACI, trans-arterial chemoinfusion; SIRT, selective internal radiation therapy.

Table 2 Summary of patient characteristics

Author, year	Demographics	TACE		Yttrium therapy			
		Regime	No. procedures	Median tumor size (cm)	Single session (%)	Whole hepatic therapy (%)	Mean activity
Burger (23), 2005	Male: 24%; age: 56; bilobar disease: 24%; extrahepatic metastasis: 12%	Variable	2	NR	NA	NA	NA
Herber (27), 2007	Male: 33%; age: 63.6; bilobar disease: 60%; extrahepatic metastasis: 0%	Lipiodol (10mL) and mitomycin (10 mL)	3.9	10.8	NA	NA	NA
Aliberti (34), 2008	Male: NR; age: 68.5; bilobar disease: NR; extrahepatic metastasis: NR	DC beads loaded with doxorubicin	3	6.5	NA	NA	NA
Gusani (35), 2008	Male: 50%; age: 58.8; bilobar disease: NR; extrahepatic metastasis: NR	Gemcitabine, gemcitabine then cisplatin, gemcitabine then oxaliplatin, gemcitabine + cisplatin, gemcitabine + cisplatin then oxaliplatin	3	NR	NA	NA	NA
[a]Ibrahim (18), 2008	Male: 67%; age: 68; bilobar disease: 67%; extrahepatic metastasis: 33%	NA	NA	NA	38	42	NR
Kim (36), 2008	Male: 76%; age: 62.9; bilobar disease: NR; extrahepatic metastasis: 51%	Lipiodol and cisplatin	3	8.9	NA	NA	NA
Shitara (41), 2008	Male: 59%; age: 74.5; bilobar disease: NR; extrahepatic metastasis: 85%	Mitomycin C	8	7.8	NA	NA	NA
Poggi (33), 2009	Male: 65%; age: 66.5; bilobar disease: NR; extrahepatic metastasis: NR	Oxaliplatin then CTx	TACE (1-7 cycles); CTx (3-7 cycles)	NR	NA	NA	NA
[a]Saxena (17), 2010	Male: 52%; age: 57; bilobar disease: 80%; extrahepatic metastasis: 49%	NA	NA	NA	All	80	1.76
[a]Haug (27), 2011	Male: 58%; age: 64.3; bilobar disease: NR; extrahepatic metastasis: 31%	NA	NA	NA	All	85	1.74
Kiefer (31), 2011	Male: 40%; age: 62; bilobar disease: NR; extrahepatic metastasis: 31%	Cisplatin, doxorubicin, mitomycin C, ethiodol, polyvinyl alcohol	2	NR	NA	NA	NA
Park (32), 2011	Male: 65%; age: 63.9/65.3; bilobar disease: 51%; extrahepatic metastasis: 54%	NR	2.5	NA	NA	NA	NA

Table 2 *(continued)*

Table 2 *(continued)*

Author, year	Demographics	TACE		Yttrium therapy			
		Regime	No. procedures	Median tumor size (cm)	Single session (%)	Whole hepatic therapy (%)	Mean activity
[a]Schiffman (40), 2011	Male: 38%; age: 68; bilobar disease: 33%; extrahepatic metastasis: 40%	Irinotecan or doxorubicin	1 session, 50%; median, NR	11.5	NA	NA	NA
Hoffman (19), 2012	Male: 18%; age: 65; bilobar disease: 63%; extrahepatic metastasis: 24%	NA	NA	NA	All	64	1.54
Kuhlmann (29), 2012	Male: 58%; age: 67; bilobar disease: NR; extrahepatic metastasis: 42%	Total, 14; median, NR	NR	NA	NA	NA	
	Male: 80% age: 62 bilobar disease: NR extrahepatic metastasis: 40%	Total, 14; median, NR	NR	NA	NA	NA	
	Male: 42%; age: 63; bilobar disease: NR; extrahepatic metastasis: 90%	NR	NR	NA	NA	NA	
Vogl (30), 2012	Male: 52%; age: 60.4; bilobar disease: 77%; extrahepatic metastasis: NR	Mitomycin C only, gemcitabine, mitomycin C + gemcitabine, mitomycin C + gemcitabine + cisplatin	NR	NR	NA	NA	NA
[a]Hyder (38), 2013	Male: 48%; age: NR; bilobar disease: NR; extrahepatic metastasis: 9.6%	Gemcitabine + cisplatin, cisplatin + doxorubicin + mitomycin, gemcitabine alone, cisplatin alone	2	NR	NR	NR	NR
[a]Mouli (26), 2013	Male: 54%; age: 68; bilobar disease: 36%; extrahepatic metastasis: 35%	NA	NA	NA	30	30	NR
[a]Rafi (39), 2013	Male: 37%; age: 61; bilobar disease: 42%; extrahepatic metastasis: 58%	NA	NA	NA	79	NR	1.2
Scheuerman (28), 2013	Male: 53%; age: 64; bilobar disease: 59%; extrahepatic metastasis: NR	Lipiodol + mitomycin C, doxorubicin	3	NR	NA	NA	NA
Median	Male: 52%; age: 63.3; bilobar disease: 59.5%; extrahepatic metastasis: 35%			9.2			
Range	Male: 18-76%; age: 57-74.5; bilobar disease: 24-80; extrahepatic metastasis: 9.6-85			6.5-11.5			

[a], SIRT. CTx, systemic chemotherapy; DEBTACE, drug eluting beads TACE; N, not applicable; NR, not reported; TACE, trans-arterial chemoembolization; TACI, trans-arterial chemoinfusion; SIRT, selective internal radiation therapy.

Patient characteristics (Table 2)

The median age at the time of each study was between 56 and 68. The mean follow-up period was 13.7 (1.9-29) months.

The majority of patients had bilobar disease 59.5% (24-77%). Extra-hepatic metastases were present in 35% (12-85%) of patients with 35% (27-100%) of patients having received previous chemotherapy. Prior liver resection was undertaken in 11.6% (11-40%) of patients. Post-procedure chemotherapy was administered in eight studies (17,28,33,35,36,38,40,41).

Assessment of outcomes (Table 3)

Follow-up occurred for 13.3 [8-29] months after therapy and radiological tumor response was recorded using Response Evaluation Criteria In Solid Tumors (RECIST) in all studies. The average reported RECIST value for complete and partial response (PR) was 6% (0-35%) and 22.4% (7-90%), respectively. The time to tumor progression was 8.2 (1.8-10) months with a median overall survival of 13 (9.1-30) months amongst all treatment modalities. Median overall survival in studies using radioembolization was 12.5 months and in studies using chemoembolization was 13 months. Overall 1-year survival for all treatments was 53.5 [40-78] months [median: SIRT 54.5% (40-61%), TACE 53% (38-78%)].

Treatment toxicity (Table 4)

Table 4 summarizes adverse effects associated with trans-arterial therapies. Side effects related to post-embolization syndrome in several studies occurred within the first few days of treatment (27,31,36,40). Other complications were reported within 30 days of treatment. Delayed toxicity was not reported. The overall rate of acute toxicity was 34.9% (26.2-89%). Twelve studies graded the severity of toxicities (17-19,23,27,31,32,35,38-41). Of those who experienced treatment toxicities, 64.3% (38-79%) were considered mild and resolved without intervention (31,35,39,40).

The most frequent clinical toxicities were abdominal pain 40% (4-100%), nausea and vomiting 27% (6.1-95%), and fatigue 19% (0-75%) (17-19,26,27,34,37). The incidence of gastroduodenal ulcers was 3% (0-20%) and did not require invasive treatment (17,18,26,27,32,37). Only one study by Shitara *et al.* reported 5% of perforated duodenal ulcer resulting in discontinuation of therapy (41). Serological toxicities included hematological abnormalities and deranged liver function test (LFT) results. Other complications reported were hepatic abscesses, acute myocardial infarction (AMI) and pulmonary embolism. Importantly, there were no deaths due to treatment toxicities.

Prognostic factors (Table 5)

Increased multiplicity, localization and vascularity of the tumor were identified as factors associated with poor overall survival (17,26,30,35,43). Whilst multiple and infiltrating tumor was a negative prognostic factor for SIRT, Mouli, 2013 #114; Saxena, 2010 #35; Hoffmann, 2012 #21 hypovascularity of the tumor was associated with poor outcome with TACE (30,43). Worse performance status as measured by Eastern Cooperative Oncology Group (ECOG) scale was a significant prognostic factor in studies assessing SIRT but not in those with chemotherapy-based treatments (17-19). Data on prognostic factors was scarce and there was inconsistency across the studies.

Discussion

Summary of evidence and interpretation

The ideal approach to treatment of inoperable disease is poorly defined. TAE therapies are a novel and increasingly performed approach for treating unresectable ICC. Outcomes are promising, but there is no standardized protocol for treatment regime, combination of agents and patient selection. Studies have examined clinical outcomes of various chemotherapeutic and radioactive agents, on their own or in combinations, but with inconsistent results (29,30,35). Combination treatment of TACE and TACI has also been reported (23,43). A potential alternative to Y90 radioembolization is DEBTACE. Four studies in this review have compared this treatment with conventional TAE therapies (29,34,38,40).

Patient characteristics of the studies summarized in this review confirm that trans-arterial therapies are offered to a variety of patients with incurable disease. A significant proportion of patients in this review had advanced disease with bilobar tumors and extra-hepatic metastases. About 35% to 100% of patients received chemotherapy prior to trans-arterial treatment. In 10% to 40% of patients, hepatic resection had already been performed. The survival benefit achieved by trans-arterial therapies across a variety of

Table 3 Results of included studies

Author, year	Treatment	Response (RECIST) %				Progression-free survival (months)	Overall survival						Key points
		CR	PR	SD	PD		Median (months)	6 months (%)	1 year (%)	2 years (%)	3 years (%)	5 years (%)	
Burger (23), 2005	TACE	75% tumor necrosis on magnet resonance imaging in 44%. PR not achieved				NR	23	95	78	30	NR	NR	Well-tolerated by 82%
Herber (37), 2007	TACE	0	7	70	27	NR	21	NR	51	27.5	27.5	NR	TACE is a safe procedure with a moderate number of complications for inoperable CCA
Aliberti (34), 2008	TACE + DEBTACE	10	90	0	0	NR	13	100	76	NR	NR	NR	A response rate of 100% on RECIST. Well tolerated by all patients
Gusani (35), 2008	TACE	0	0	57	43	NR	9.1	65	38	14	4	0	Median survival with gemcitabine-cisplatin combination TACE had significantly longer survival (13.8 months) compared gemcitabine alone (6.3 months)
[a]Ibrahim (18), 2008	SIRT	9 (EASL)	27 (EASL)	68 (EASL)	NR	NR	14.9	NR					Baseline ECOG is a prognostic factor for survival. The median survival for patients with an ECOG performance status of 0, 1, and 2 was 31.8 months, 6.1 months, and 1 month, respectively
Kim (36), 2008	TACI, TACE	35	20	NR	NR	10	12	NR	46	38	30	NR	55% clinical success
Shitara (41), 2008	TACI	5	45	0	10	8.3	14.1	NR					The response rate was 50.0%. Median survival was 14.1 months

Table 3 *(continued)*

Table 3 *(continued)*

Author, year	Treatment	Response (RECIST) %				Progression-free survival (months)	Overall survival						Key points
		CR	PR	SD	PD		Median (months)	6 months (%)	1 year (%)	2 years (%)	3 years (%)	5 years (%)	
Poggi (33), 2009	Oxaliplatin eluting microspheres-TACE	0	44	56	0	8.4	30	NR	NR	NR	NR	NR	Significantly increased overall survival with no major adverse events. Decrease in tumor size
[a]Saxena (17), 2010	SIRT	0	26	48	22	NR	9.3	56	40	27	13	NR	Two factors were associated with an improved survival: peripheral tumor type and ECOG status of 0.
[a]Haug (27), 2011	SIRT	NR	22	65	13	NR	12.5	79	53	31	NR	NR	FDG PET/CT was able to predict patient outcome after radioembolization treatment, with the change in metabolically active tumour volume at 3 months being the best independent predictor. High tumour vascularization was not a prerequisite for successful radioembolisation
Kiefer (31), 2011	TACE	0	7	60	27	NR	21.1	NR	51	27.5	27.5	NR	Median survival from time of first chemoembolization was 15 months
Park (32), 2011	TACE	0	23	67	11	NR	12.2	76	51	12	10	5	Survival period was longer in the TACE group (median 12.2 months) than in the symptomatic treatment (median 3.3 months) group
[a]Schiffman (40), 2011	DEBTACE	6	6	72	17	NR	17.5	NR					DEBTACE is safe and effective, providing a marked survival benefit when DEB therapy is used as adjunctive therapy to systemic CTx

Table 3 *(continued)*

Table 3 *(continued)*

Author, year	Treatment	Response (RECIST) %				Progression-free survival (months)	Overall survival						Key points
		CR	PR	SD	PD		Median (months)	6 months (%)	1 year (%)	2 years (%)	3 years (%)	5 years (%)	
Hoffman (19), 2012	SIRT	0	36	52	15	9.8	22	83	61	41	12	0	Predictors for prolonged survival are performance status, tumor burden and RECIST response
Kuhlmann (29), 2012		NR NR NR	4 10 26	42 10 45	50 60 29	3.9 1.8 6.2	11.7 5.7 11.0	NR					This is the first study demonstrating that DEBTACE-TACE is safe in patients with normal liver function, and results in a prolongation of PFS and OS. Local tumor control, PFS and OS similar to systemic ChT with oxaliplatin and gemcitabine, but superior to cTACE
Vogl (30), 2012	TACE	0	9	57	34	NR	13	NR	52	29	10	8	No statistically significant difference between patients treated with different chemotherapy protocols was noted
[a]Hyder (38), 2013	Total SIRT TACE	3.1 34.6 (EASL)	NR	61.5 47.5 (EASL) NR	13	NR	13.2 11.6 13.4	NR NR	54	NR	22	16	Similar results across different types of trans-arterial therapy
[a]Mouli (26), 2013	SIRT	0	2.5 (WHO), 9 (EASL)	73 (WHO), 64 (EASL)	2 (WHO), 0 (EASL)	NR	Overall: 14.6 Multifocal: 5.7 Infiltrative: 6.1 Bilobar: 10.9	NR					Solitary tumor is a prognostic factor with tumor reduction allowing conversion to surgical resection for curative therapy

Table 3 *(continued)*

Table 3 *(continued)*

Author, year	Treatment	Response (RECIST) %				Progression-free survival (months)	Overall survival						Key points
		CR	PR	SD	PD		Median (months)	6 months (%)	1 year (%)	2 years (%)	3 years (%)	5 years (%)	
[a]Rafi (39), 2013		0	11	68	21	NR	11.5	67	56	10	0	0	No deaths within 30 days
Scheuerman (28), 2013	TACE	NR	NR	NR	NR	NR	11	64	42	26	15	8	There is no significant survival benefit of surgery in lymph node positive patients or positive resection margin over TACE
Median	All	6	22.4	60	19.5	8.15	13		53.5				
	TACE/TACI	10	20	57	15	8	13		53				
	SIRT	0	25.5	66.5	15	9.8	12.5		54.5				
Range	All	3.1-35	6-44	10-72	5-43	1.8-9.8	5.7-30		38-78				

[a], SIRT. CR, complete response; CTx, systemic chemotherapy; DEBTACE, drug eluting beads TACE; EASL, European Association for the Study of Liver Tumor Response Criteria; NR, not reported; PR, partial response; RECIST, Response Evaluation Criteria In Solid Tumors; TACE, trans-arterial chemoembolization; TACI, trans-arterial chemoinfusion; SIRT, selective internal radiation therapy; SR, stable response; WHO, World Health Organization Tumor Response Criteria.

Table 4 Summary of toxicity after trans-arterial therapies

Author, year	Treatment	Acuity (days)	Toxicity (%)								Severity	
			Overall	Fatigue	Abdominal pain	Nausea/ vomiting	Haematological	GIT ulcers	Deranged LFTs	Other	Grade 1-2	Grade 3-4
Burger (23), 2005	TACE	<30	17	NR	6	NR	NR	NR	NR	NR	NR	6
Herber (37), 2007	TACE	<30	40	NR	40	27	NR	7		Hepatic arteries spasm 13; anaphylactic shock 7	NR	NR
Aliberti (34), 2008	TACE + DEBTACE	<30	NR	0	100	95	0	0		Neoplastic fever 100; hepatic abscess 3	NR	NR
Gusani (35), 2008	TACE	<30	NR	NR	NR	NR	Thrombocytopenia 5	NR	Bilirubin 5	AMI 2; hepatic abscess 2	38	17
[a]Ibrahim (18), 2008	SIRT	NR	NR	75	38	17	NR	4	Bilirubin (grade 3) 4; albumin (grade 3) 71	NR	NR	4
Kim (36), 2008	OEM-TACE	10	NR	NR	NR	NR	NR	NR	NR	Most had post-embolization syndrome which resolved	NR	NR
Shitara (41), 2008	TACI	NR	NR	NR	NR	NR	Neutropenia 4	20; perforated 5		Gastritis 6, cholangitis 6	NR	6
Poggi (33), 2009	Oxaliplatin eluting microspheres-TACE	<30	NR	0	42	30	0	0	30	Peripheral neuropathy 4; cholangitis 1.5; hypertensive crisis 1.5	NR	NR
[a]Saxena (17), 2010	SIRT	<30	NR	64	40	Nausea 16, vomiting 8	0	4	Albumin 8, bilirubin 4	Alkaline toxicity 4; anorexia 16; ascites 16; pleural effusion 8; pulmonary embolism 4	NR	4
[a]Haug (27), 2011	SIRT	2	NR	NR	58	Nausea 50; vomiting 19	0	8	0	NR	NR	0
Kiefer (31), 2011	TACE	1	65	NR	NR	NR	NR	NR	NR	Post-embolization syndrome 65	65	3% APE
Park (32), 2011	TACE	<30	NR	NR	4	1	13	13	AST 2.3; ALT 1.1; ALP 2.3; bilirubin 11.2; hypoalbuminemia 5.7	NR	NR	37

Table 4 *(continued)*

Table 4 *(continued)*

Author, year	Treatment	Acuity (days)	Toxicity (%)								Severity	
			Overall	Fatigue	Abdominal pain	Nausea/ vomiting	Haematological	GIT ulcers	Deranged LFTs	Other	Grade 1-2	Grade 3-4
[a]Schiffman (40), 2011	TACE	1-3	26.2	NR	NR	NR	NR	NR	Hepatorenal syndrome 4	Post-embolization syndrome 27; pneumonia 4; atrial fibrillation 8	63.6	36.3
Hoffman (19), 2012	SIRT	NR	NR	NR	85	Nausea 61; vomiting 27	0	0	Bilirubin 70; AST 55; ALT 33	NR	NR	0
Kuhlmann (29), 2012	TACE + DEBTACE	NR	NR	NR	69	0	0	0	NR	Hepatic abscess 4; pleural empyema 4	NR	NR
	TACE	NR	NR	10	50	30	0	0	Liver failure 10	Hypertension 20; urticaria 10; pulmonary embolism 10; cholangitis 10	NR	NR
	CTx	NR	NR	NR	NR	NR	Febrile neutropenia 6	NR	NR	Death 10; peripheral neuropathy 19	NR	NR
Vogl (30), 2012	TACE	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
[a]Hyder (38), 2013	Various	NR	29.8	17	12.1	6.1	0	0	Jaundice 2; hepatorenal syndrome 8	NR	NR	16
[a]Mouli (26), 2013	SIRT	NR	NR	54	28	Nausea 13; vomiting 9	NR	2	Albumin (grade 3) 9; bilirubin (grade 3) 7	Ascites 15; pleural effusion 4	NR	NR
[a]Rafi (39), 2013	SIRT	NR	89	21	32	0	5	0	32	21	79	11
Scheuerman (28), 2013	TACE	NR	NR	NR	NR	NR	NR	NR	Liver failure 2	Septic shock 2; multiple organ failure 4; AMI 11	NR	NR
Median			34.9	19	40	27	4	3	Liver failure 4	-	64.3	8.5
Range			26.2-89	0-75	4-100	6.1-95	0-13	0-20	2-10	-	38-79	0-37

[a], SIRT. AMI, acute myocardial infarction; APE, acute pulmonary edema; CTx, systemic chemotherapy; DEBTACE, drug eluting beads TACE; LFT, liver function test; NA, not applicable; NR, not reported; TACE, trans-arterial chemoembolization; TACI, trans-arterial chemoinfusion; SIRT, selective internal radiation therapy.

Table 5 Clinical and pathological factors associated with poorer overall survival on univariate analysis

Factors	Association with poorer overall survival	
	Significant	Non-significant
Tumor type (infiltrating *vs.* peripheral)	[a]Mouli (26), [a]Saxena (17), Gusani (35): 3 studies	Vogl (30), Kim (36): 2 studies
ECOG	[a]Hoffman (19) (0 *vs.* 1,2), [a]Saxena (17) (0 *vs.* ≥1), [a]Ibrahim (0 *vs.* 1,2) (18): 3 studies	Park (32): 1 study
Number of lesions (multifocal)	[a]Mouli (26): 1 study	Vogl (30): 1 study
Location of lesions		Park (32), Kim (36)
Tumor burden	[a]Hoffman (19): 1 study	Park (32): 1 study
Tumor hypovascularity	Kim (36), Vogl (30): 2 studies	Park (32): 1 study
Extra-hepatic disease	Park (32): 1 study	Kiefer (31): 1 study
RECIST	[a]Hoffman (19) (partial response P<0.001), Gusani (35), Park (32), Vogl (stable disease P<0.001) (30): 4 studies	
TACE regime	Gusani (35) [gemcitabine-cisplatin *vs.* gemcitabine alone (13.8 *vs.* 6.3 months, P=0.0005]: 1 study	Vogl (30): 1 study
Treatment regimes		
TACE *vs.* TACI *vs.* TACE + TACI	Kim (TACI alone P<0.001) (36): 1 study	
TACE + DEBTACE *vs.* TACE or systemic chemotherapy		Kuhlmann (29): 1 study
Child pugh class (B *vs.* A)	Vogl (Child Pugh B) (30): 1 study	Kim (36): 1 study
Previous chemotherapy		[a]Hoffman (19): 1 study
Previous surgery		[a]Hoffman (19): 1 study
Portal vein thrombosis	[a]Ibrahim (18): 1 study	

[a], SIRT. AMI, acute myocardial infarction; APE, acute pulmonary edema; CTx, systemic chemotherapy; ECOG, Eastern Cooperative Oncology Group Performance Status; DEBTACE, irinotecan drug eluting beads; LFT, liver function test; NA, not applicable; NR, not reported; SIRT, selective internal radiation therapy; TACE, trans-arterial chemoembolization; TACI, trans-arterial chemoinfusion.

patient groups shows these treatments are highly effective. However, the inconsistencies in patient demographics reflect the lack of specific patient selection criteria for trans-arterial therapies and results should be interpreted in the context of this potential bias.

Our review showed that TACE, TACI and SIRT achieved similar rates of tumor response in unresectable ICC (*Table 3*). Seven studies used radioembolization (17-19,26,27,38,39). Although none of these studies reported complete tumor response, rates for partial and stable response (SR) were higher than the average value reported by studies using chemoembolization. Overall and 1-year survival rates were also similar between the chemotherapy-based and radiotherapy-based approaches. Median overall survival was 13 months. This is higher than median overall survival of 11 months for systemic chemotherapy, reported in the recent metaanalysis (11). In two studies, tumor reduction following trans-arterial therapy allowed surgical resection of the tumor (23,40). Surgical resection following trans-arterial therapy allows the possibility of cure for previously unresectable ICC.

With advances in treatment techniques and clinical outcome, recent focus has shifted to maximizing clinical efficacy by using combination of trans-arterial approaches, drugs and radioactive agents. Combination of various chemoinfusion and TACE protocols was applied upon case-by-case assessments by Burger *et al.*, who reported the highest overall survival of 30 months (23). However, their study was limited by a small sample size and absence of control groups. Another study by Kim *et al.* supports that combination therapy may enhance efficacy of TACI (36). Whilst TACI alone was a significant negative prognostic

factor for overall survival, concomitant TACI and TACE achieved similar clinical success toTACE alone (36). Kuhlmann *et al.* compared systemic chemotherapy, TACE and DEBTACE, and found that combination therapy with TACE and DEBTACE is superior to both TACE and systemic chemotherapy alone (29).

Chemotherapy agents used across 13 studies using TACE and/or TACI varied widely; drugs included cisplatin, doxorubicin, gemcitabine, 5-fluorouracil, irinotecan, mitomycin C and oxaliplatin. Results on the optimal drug combination are controversial. Gusani *et al.* stated combination therapy using gemcitabine/cisplatin/oxaliplatin were most beneficial for overall survival (35), but another study found no significant differences among drug combinations (30). Overall survival of 23 and 21 months were demonstrated in studies using oxaliplatin (33) and mitomycin (37), respectively. However, a quantitative analysis is needed to assess its significance.

There are many studies analyzing predictors of survival in resectable ICC (44,45), but data is limited on trans-arterial treatment of inoperable disease. Identifying prognostic factors can optimize patient selection and improve treatment outcomes. Currently, patient selection criteria for trans-arterial therapies are unclear (17,36). Prognostic factors differed between chemo- and radio-embolization. ECOG status prior to treatment (17,19), multiple or bilobar tumors (26) and greater tumor burden/volume (19) were negatively associated with SIRT outcomes whereas hypovascularity of the tumor (30,36) and extra-hepatic involvements (32) were predictors of poor prognosis with TACE. Poor Child Pugh Class at treatment was also associated with poorer outcomes after TACE (30). These observations may be related to the rationale behind the different trans-arterial approaches. TACE exploits the fact that tumor draws most of its blood supply from the hepatic artery; hypervascular tumor may allow greater drug delivery and hence higher drug concentration (5). However, in light of the overall benefits of TAE and inadequate evidence, patients with hypovascular tumour should not be denied therapy until more evidence is acquired (36). SIRT delivers radioactive particles selectively and deeply within the tumor bed, hence greater tumor volume and multiplicity may require higher radiation doses and wider range of exposure risking unwanted toxicity (5). Assessment of tumor vascularity in TACE and measurement of tumor burden may identify ideal treatment options for patients with unresectable ICC.

TAE is safe with mild to moderate toxicity. Overall 30-day mortality in this study was 0.6% which is consistent with the most recent rate of 0.7% reported in a meta-analysis (16). Studies in our review reported acute toxicity rate of 34.9%. The majority of post-procedural complications was within 30 days and resolved without intervention. The most common types of adverse effects in both chemo- and radio-embolization were abdominal pain, nausea and vomiting and fatigue. Mild to moderate gastrointestinal ulcers and derangements in liver function were also relatively common. Haematological complications were more prevalent following TACE and systemic chemotherapy (CTx). Hepatic abscesses were also only observed in patients undergoing TACE (34,35,46). This may be confounded by the higher prevalence of hematological toxicities including neutropenia. Although the trans-arterial approach allows more targeted delivery of drugs and radiation without unwanted toxic exposure, a degree of systemic toxicity may be inevitable. Nonetheless, delayed toxicity was not recorded in any of the studies and acute complications were mostly mild and resolved spontaneously. The reporting of adverse events was inconsistent between studies and not all studies graded treatment toxicity. There was also discrepancy in the acuity of complications. A standardized approach to assessment of adverse outcomes may be useful to allow more accurate comparisons of safety data.

Despite the growing evidence on the therapeutic potential of TAE, there is only one systematic review to date evaluating the safety and efficacy of only chemotherapy-based treatments (16). However, in that study, no limitations in study design or publication dates were applied in their search, and the final selection of studies included abstracts for meetings and conferences. Although our study does not include a metaanalysis, we opted for meticulous selection of eligible studies using specific search criteria. In addition, meta-analysis of inappropriate and significantly heterogeneous data is not a necessary part of systematic reviews and the results of any metananalysis of such data should be interpreted with caution (47). To our knowledge, this is also the first review to assess all modalities of trans-arterial therapy including radioembolization.

Review limitations

The main limitation of this study was that meta-analysis could not be performed due to statistical, methodological and clinical heterogeneity. In particular, the heterogeneity of patient demographics, tumor pathology and treatment

modality resulted in significant variation in results. Much of this is due to the lack of standardized treatment protocols. However, this review summarizes the best available evidence and provides useful information on the efficacy and safety of trans-arterial therapies for unresectable ICC.

Guidelines for future studies

This review demonstrates the lack of appropriate and consistent data required for meta-analysis. Prospective studies with pre-determined and standardized data assessment will be needed. This will facilitate consistent patient selection criteria and outcome measures providing appropriate volume and quality of data to accurately assess patient and disease characteristics and treatment outcomes including safety profile. There was no randomized controlled trial on trans-arterial therapies identified by our search. Future randomized studies are required to assess efficacy of combined trans-arterial therapies and the use of adjuvant systemic therapies in trans-arterial therapies. Specific drug combinations and therapy protocols need to be investigated further to assess the ideal treatment option for patients.

Conclusions

Trans-arterial therapies are safe and effective treatment options for unresectable ICC. They confer improvement in overall survival and achieve tumor reduction, allowing curative surgical resection in some cases. Although no specific patient selection criteria or prognostic factors for treatment success exists, the results of this review suggest that there are various patient and disease factors associated with clinical outcome. In the absence of large randomised controlled trials, these findings must be considered in conjunction with clinical decision making tailored to each patient.

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Footnote

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