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Locoregional therapies in patients with intrahepatic cholangiocarcinoma: A systematic review and pooled analysis

Julien Edeline [a,*], Angela Lamarca [b], Mairéad G. McNamara [c], Timothy Jacobs [d], Richard A. Hubner [b], Dan Palmer [e], Bas Groot Koerkamp [f], Philip Johnson [e], Boris Guiu [g], Juan W. Valle [c]

[a] Department of Medical Oncology, Centre Eugène Marquis, Rennes, France
[b] Department of Medical Oncology, The Christie NHS Foundation, Manchester/Division of Cancer Sciences, University of Manchester, Manchester, United Kingdom
[c] Division of Cancer Sciences, University of Manchester/Department of Medical Oncology, Manchester, United Kingdom
[d] The Library, The Christie NHS Foundation Trust, Manchester, United Kingdom
[e] University of Liverpool, Liverpool, United Kingdom
[f] Department of Surgery, Erasmus MC Cancer Institute, Rotterdam, Netherlands
[g] Departement of Radiology, St-Eloi University Hospital, Montpellier, France

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ABSTRACT

Background: Locoregional treatments (LRT) including radioembolisation (SIRT), transarterial chemoembolisation (TACE), hepatic arterial infusion (HAI) of chemotherapy, external beam radiotherapy (EBRT) and ablation have been studied for the management of intrahepatic cholangiocarcinoma (iCC). The aim of this systematic review was to provide outcome benchmarks for clinical trial design.

Methods: Identification of studies reporting outcomes of patients treated with LRT for iCC was performed using PubMed and Embase. Pooled weighted means were calculated for progression-free survival (PFS) and overall survival (OS); meta-analysis of proportions was used for estimation of pooled response rate.

Results: 6325 entries were reviewed; 93 studies were eligible, representing 101 cohorts and 3990 patients: 15 cohorts (645 patients) for ablation, 18 cohorts (541 patients) for EBRT, 27 cohorts (1232 patients) for SIRT, 22 cohorts (1145 patients) for TACE, 16 cohorts (331 patients) for HAI and 3 cohorts (96 patients) not pooled. 74% of the studies were retrospective, 99% non-randomised.

The pooled mean weighted OS was 30.2 months (95% confidence interval (CI): 21.8–38.6) for ablation, 18.9 (14.2–23.5) for EBRT, 14.1 (12.1–16.0) for SIRT, 15.9 (12.9–19.0) for TACE and 21.3 (15.4–27.1) for HAI. The pooled complete response rate was 93.9% for ablation. When analysed together, SIRT, TACE and HAI had a pooled mean weighted OS of 15.7 months, and 25.2 months for patients treated in first-line with concomitant systemic chemotherapy.

Conclusions: Available literature on LRT for iCC was heterogeneous and of insufficient quality to make strong recommendations. Ablation achieved satisfactory outcomes, and may be recommended when surgery is not feasible.

Introduction

Intrahepatic cholangiocarcinoma (iCC) has a rising incidence in Western countries [1]. Due to its relative rarity, treatment strategies utilising systemic therapies are mostly derived from the results of prospective trials including all biliary tract cancers (BTC) of different origins [2,3]. However, iCC might present a different biology and prognosis, compared with other origins of BTC (i.e. perihilar or distal

Abbreviations: BTC, Biliary Tract Cancers; CI, Confidence Interval; EBRT, External beam Radiotherapy; HAI, Hepatic Arterial Infusion; IAT, Intra-arterial Therapies; iCC, Intrahepatic cholangiocarcinoma; LRT, Locoregional treatments; MeSH, Medical Subject Headings; NCI-CTCAE, National Cancer Institute, Common Terminology Criteria for Adverse Events; OS, Overall Survival; PFS, Progression-Free Survival; RECIST, Response Evaluation Criteria in Solid Tumors; SIRT, Selective Internal Radiation Therapy; TACE, Trans-arterial (chemo-)embolisation.

* Corresponding author.
E-mail address: j.edeline@rennes.unicancer.fr (J. Edeline).

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cholangiocarcinoma or gallbladder cancer) [4]. Moreover, locally-advanced and metastatic BTC are frequently pooled in the same studies as advanced BTC. Outcomes of patients with liver-only iCC are significantly better than outcomes of unselected patients with advanced BTC, with a median overall survival (OS) of 16.7 months (95% confidence interval (CI): 8.7 to 20.2 months) vs 11.7 months (95% CI: 10.2–12.6) in the post-hoc analysis of patients treated with cisplatin-gemcitabine in the Advanced Biliary tract Cancer (ABC)-01, ABC-02 and ABC-03 trials [4].

As unresectable iCC frequently presents as a liver-only or liver-predominant disease, loco-regional treatments (LRT) have been applied in these settings [5]. LRT studied in iCC range from ablation techniques (used for resectable tumours, but frequently in specific context) to external beam radiotherapy (EBRT) to intra-arterial therapies (IAT). These in turn include trans-arterial (chemo-)embolisation (TACE), selective internal radiation therapy (SIRT, also known as radioembolisation) and hepatic arterial infusion of chemotherapy (HAI), which have different mechanisms of action. LRT have been advocated in guidelines of treatment of iCC or BTC, either as a first-line option, or after progression following first-line systemic chemotherapy [6,7]. However, the available studies exploring its use are heterogeneous, both in regards to the population included and the results obtained; hence, the real benefit derived for LRT in iCCA remains unclear. Previous systematic reviews have tried to address the role of LRT in iCC, but did not study the whole spectrum of LRT and many do not include all the currently-available literature [8–10].

We thus performed a systematic review of the existing literature regarding the use of LRT in patients with iCC.

Methods

Objectives

This systematic review and pooled analysis aimed to: 1- summarise the current literature relating to the different LRT employed in the treatment of patients with iCC, 2- describe the quality of evidence based on the current literature for the different LRT, 3- provide outcomes as a benchmark for future clinical trial design. This systematic review and pooled analysis was registered in PROSPERO under the ref CRD42020210017 before any search was conducted and followed the PRISMA guidelines.

Search strategies

The search in PubMed was last updated on October 9th 2020 using the following strategy: (“Radioembolization” OR “radioembolisation” OR “TARE” OR “SIRT” OR “Yttrium-90” OR “Selective Internal radiation therapy”) OR (“chemoembolization” OR “chemoembolisation” OR “TACE” OR “Transarterial embolization” OR “TAE”) OR (“hepatic arterial infusion” OR “HAI” OR “Infusions, intra-arterial” (MeSH term)) OR (“external beam radiotherapy” OR “stereotactic radiotherapy” OR “SBRT” OR “EBRT” OR “proton” OR “radiotherapy” (MeSH term)) OR (“Radiofrequency” OR “Ablation” OR “Microwave” OR “RFA” OR “MWA” OR “Ablation techniques” (MeSH term) OR “Radiofrequency ablation” (MeSH term)) OR (“trans-arterial” OR “transarterial” OR “loco-regional” OR “locoregional” OR “embolization” OR “embolisation”) AND “cholangiocarcinoma” (MeSH term). The search in EMBASE was performed on November 11th 2020 and used the following strategy: 1- (“Radioembolization” or “radioembolisation” or “Radio embolization” or “radio embolisation” or “TARE” or “SIRT” or “Yttrium-90” or “Selective Internal radiation therapy”), 2-(“chemoembolization” or “chemoembolisation” or “chemo embolization” or “chemo embolisation” or “TACE” or “Transarterial embolization” or “TAE”), 3-(“hepatic arterial infusion” or “HAI”), 4-(“external beam radiotherapy” or “stereotactic radiotherapy” or “stereotactic radiosurgery” or “Stereotactic Body” or “SBRT” or “EBRT” or “proton*” or CyberKnife or srs or “gamma knife”), 5-exp intraarterial drug administration, 6-exp radiotherapy, 7-(“trans-arterial” or “transarterial” or “loco-regional” or “locoregional” or “embolization” or “embolisation”), 8–1 or 2 or 3 or 4 or 5 or 6 or 7, 9-(cholangiocarcinoma* or (“bile duct*” adj2 cancer*)), 10-exp bile duct carcinoma, 11–9 or 10, 12–8 and 11.

Potentially eligible studies were selected from the 2 aforementioned searches by reviewing the abstracts and when necessary the full text. All studies meeting the inclusion criteria were included, even when a complete manuscript was not available.

Study eligibility

Inclusion criteria for the systematic review included: studies involving patients treated for iCC not amenable to surgery, treated with LRT, including SIRT, TACE, trans-arterial embolisation, HAI chemotherapy, EBRT and ablation; studies available in PubMed and/or Embase from January 2000 to the date of search. Exclusion criteria were the following: studies including patients with all types of BTC without distinction of outcomes for iCC, studies pooling results of different LRT, without distinction of outcomes for each of them, studies with number of patients less than 10, studies including patients with resected tumours or resectable patients treated with a neoadjuvant strategy, studies published in a language other than English, studies not reporting at least one of the following outcomes: radiological response by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, progression-free survival (PFS), liver-specific-PFS, OS, and grade 3–4 toxicity according to National Cancer Institute – Common Terminology Criteria for Adverse Events (NCI-CTCAE).

In case of duplicates (i.e. 2 studies with the same author including the same population), selection of the publication with the largest number of patients was made, and the other was discarded. When the author appeared on both a single-centre and a multicentre study using the same cohort of patients, the multicentre study was selected and the single-centre study was excluded.

Selection of studies and data extraction was performed by one author (JE), and for studies for which inclusion was unclear, inter-reviewer agreement was utilised (including two other authors: AL and JWV). Disagreement was resolved by consensus (all 3 authors).

Data extraction and evaluation of the risk of bias

The following items were evaluated for risk of bias assessment: 1-study design; 2- definition of the study population and definition of the intervention; 3- existence of an appropriate control: and 4- definition of the outcomes (Supplementary Table 1). Each of these items was scored as “low-“, “intermediate-“ or “high” risk of bias. Overall, a study was considered as low risk of bias if at least 2 of the items were classified as low risk, and no high risk item was present; it was considered as high risk of bias if at least 2 of the items were classified as high risk of bias; and was considered as intermediate risk in the other situations. If a study was available only in abstract form, its risk of bias was increased by one level.

Pooled description of study design and included patient population

The following data were collected from articles and pooled overall and for each LRT: study characteristics (prospective vs retrospective, number of patients, existence of a control group), patient demographics, presence of cirrhosis, performance status, previous treatment (chemotherapy, surgery, biliary drainage), extent of the disease (size of largest lesion, unilobar vs bilobar; unifocal vs multifocal; portal vein invasion; extra-hepatic spread; presence of lymph nodes or visceral metastases); characteristics of the treatment (including use of concomitant systemic chemotherapy, defined as the use within a single strategy); outcomes as previously described. As some studies included more than one cohort of patients (either treated with different LRT or corresponding to a

different population), descriptive analysis of the design of the studies were presented per study; while descriptive analysis of the population included were presented per cohorts.

Statistical analysis: pooled outcomes and meta-analyses

Outcome data analyses were performed for each subtype of LRT separately; in addition, outcome data jointly for IAT (SIRT, TACE and HAI) were also analysed. Studies using a combination of 2 LRT in the same cohort of patients were not pooled, but results are presented in the descriptive analysis. Statistical analysis was performed using STATA v.12 software (Stata Corporation, College Station, TX, USA). Meta-analysis of proportions was used for estimation of pooled weighted frequency (percentage (%)) (metaprop command, Stata v.12), employing random effects model, rather than fixed effects model, since heterogeneity between studies was expected to be present. Heterogeneity, in the form of the inconsistency (I^2 index) and p-value, was also reported; a statistically significant p-value < 0.05 being indicative of a problem with heterogeneity. This approach was used for calculation of pooled response rate, pooled complete response rate and pooled disease control rate using the number of response-evaluable patients in each study as the denominator. For the calculation of pooled secondary resection rate, the number of patients in each study was used as the denominator. Pooled weighted mean and 95% CI were calculated for PFS, liver PFS and OS, weighted according to the number of patients with iCC included in each study (analytical weighting). The same approach was used for calculation of pooled weighted mean and 95% CI for 2-year control rate for EBRT and ablation groups.

Subgroup analyses for data on patients with liver-only disease, patients treated without previous systemic chemotherapy, and patients treated with concomitant chemotherapy were initially planned.

Results

Selection and description of studies

The PubMed search identified 1688 abstracts and the Embase search identified 4637 abstracts, of which 93 entries were eligible (Fig. 1). The main reasons for exclusion were studies outside of the scope, duplicates, reviews, number of patients less than 10 and the absence of specific data on iCC, treatment modalities or outcomes.

Finally, 93 studies corresponding to 101 cohorts (some studies including different cohorts of patients) reporting data on a total of 3990 patients were deemed eligible and included in the descriptive analysis. Of these, data on 90 studies were used for estimation of pooled outcomes and meta-analyses of proportions. Three cohorts were included in the systematic review, but results could not be pooled with other LRT: 2 cohorts with combined treatment with 2 different LRT (TACE and EBRT for one, and HAI and EBRT for the other), and 1 cohort treated with brachytherapy. The list of the included studies in the descriptive analysis, with their evaluation of risk of bias, are presented as supplementary Table 2. There was an increasing number of studies from 2014, with more than 10 studies per year in 2019 and 2020, as compared to 0 to 3 from 2000 to 2009 (Supplementary Fig. 1).

The studies included in the descriptive analysis are presented in Table 1. Of the 93 studies, 69 (74%) were retrospective, 70 (75%) were single-centre, 86 (93%) did not have an adequate control group, and 18 (19%) were available only in abstract form. Only 1 study was a randomised control trial, but results were available only in abstract form. Overall, 79 (85%) were classified as high risk of bias, 14 (15%) as intermediate risk of bias, and none as low risk of bias. The risk of bias did not clearly differ between treatment modalities, albeit HAI studies were more frequently prospective trials (7 of 14 studies, 50%).

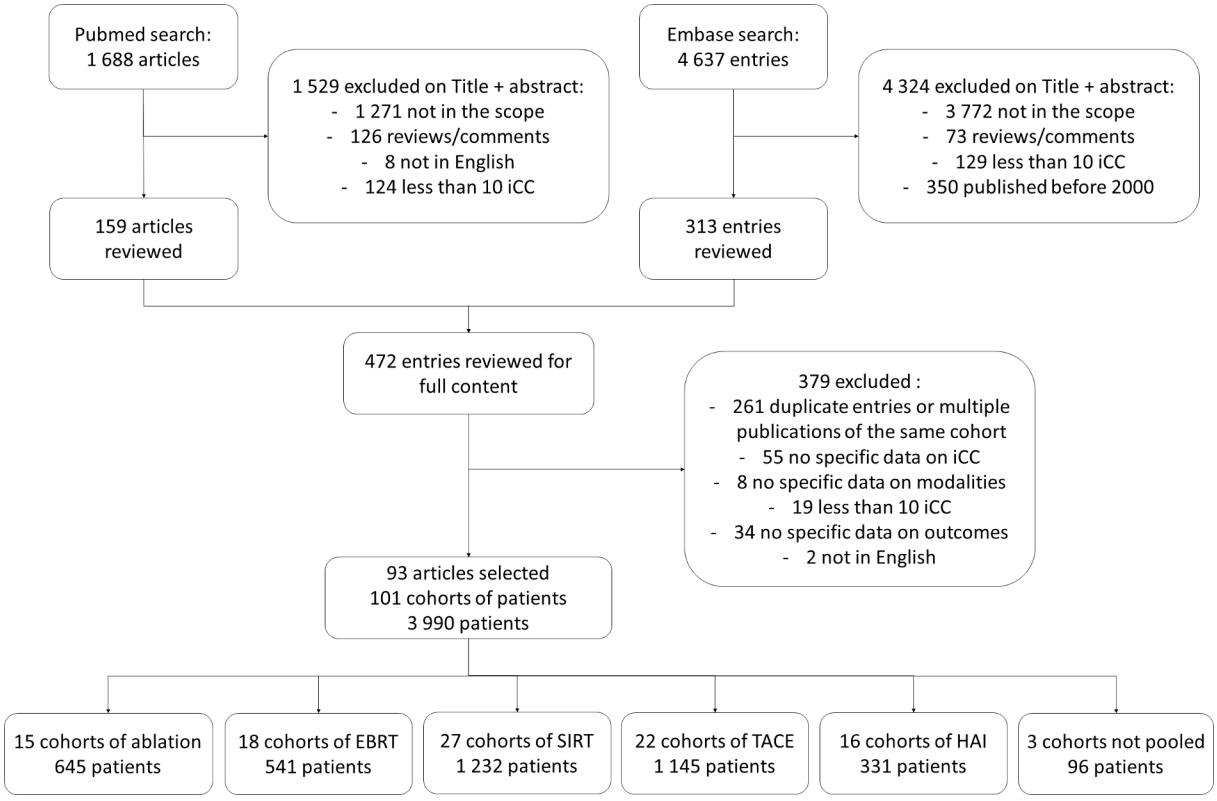

Fig. 1. PRISMA flow-chart of selection of the studies included (iCC: intrahepatic cholangiocarcinoma, EBRT: external beam radiotherapy, SIRT: selective internal radiation therapy, TACE: transarterial chemo-embolisation, HAI: Hepatic arterial infusion).

Table 1
Characteristics of the studies included.

	All studies (n = 93)	EBRT (n = 17)	Ablation (n = 14)	SIRT (n = 25)	TACE (n = 20)	HAI (n = 14)
Prospective trial	16 (17%)	3 (18%)	0 (0%)	2 (8%)	3 (15%)	7 (50%)
Prospective cohort	8 (9%)	1 (6%)	2 (14%)	3 (12%)	2 (10%)	0 (0%)
Retrospective study	69 (74%)	13 (77%)	12 (86%)	20 (80%)	15 (75%)	7 (50%)
Multicentre	23 (25%)	4 (24%)	1 (7%)	6 (24%)	9 (45%)	3 (21%)
No or inadequate control group	86 (93%)	15 (88%)	12 (86%)	25 (100%)	18 (90%)	13 (93%)
Adequate not randomised	6 (7%)	2 (12%)	2 (14%)	0 (0%)	1 (5%)	1 (7%)
Randomised	1 (1%)	0 (0%)	0 (0%)	0 (0%)	1 (5%)	0 (0%)
Clearly Defined Inclusion/Exclusion criteria	55 (59%)	9 (53%)	10 (71%)	12 (48%)	12 (60%)	10 (71%)
Clear definition of outcomes	59 (63%)	12 (71%)	11 (79%)	12 (48%)	14 (70%)	8 (57%)
Available only as abstract	18 (19%)	1 (6%)	1 (7%)	9 (36%)	5 (25%)	2 (14%)
Risk of bias Low	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Risk of bias Intermediate	14 (15%)	3 (18%)	0 (0%)	2 (8%)	3 (15%)	5 (36%)
Risk of bias High	79 (85%)	14 (82%)	14 (100%)	23 (92%)	17 (85%)	9 (64%)

EBRT: external beam radiotherapy, SIRT: selective internal radiation therapy, TACE: transarterial chemo-embolisation, HAI: Hepatic arterial infusion

Description of the cohorts of patients included

Data provided by individual studies describing the patient cohorts varied markedly between studies (Table 2), with many variables such as performance status, cirrhosis and previous biliary drainage reported in less than half of the studies. There was also heterogeneity between modalities when reporting. The median number of patients per treatment cohorts included was 25, and ranged from 10 to 183 patients. Patient characteristics differed across treatment modalities regarding the use of previous chemotherapy, previous surgery, tumour size, multifocality of the disease, macrovascular invasion, and extrahepatic spread.

Description of treatment modalities

In the ablation group, radiofrequency ablation was the LRT of choice in 7 of 15 cohorts, microwave ablation in 4, and mixed modalities in 4. No concomitant systemic chemotherapy was used. In the EBRT group, stereotactic radiation was performed in 8 of 17 cohorts, conformational in 3, proton beam in 4, carbon-ion in 1 and mixed modalities in 1. The median dose was 50 Gy (range: 30–72) in 5 to 15 fractions. Concomitant systemic chemotherapy was delivered in 158 of 217 (72.8%) patients (data from 6 cohorts). In the SIRT group, glass-microspheres were used in 7 of 24 cohorts, resin-microspheres in 12, and mixed in 5. A mean of 1.3 sessions were performed (data from 12 cohorts). Radioactive activity data were provided for 12 cohorts, but tumour dose only in 4. Concomitant systemic chemotherapy was delivered in 63 of 221 (29.9%) patients (data from 4 cohorts). In the TACE group, lipiodol (i.e.,

Table 2
Description of population of patients included in the cohorts.

	All cohorts (n = 101 cohorts, 3990 patients)	Ablation (n = 15 cohorts, 645 patients)	EBRT (n = 18 cohorts, 541 patients)	SIRT (n = 27 cohorts, 1232 patients)	TACE (n = 22 cohorts, 1145 patients)	HAI (n = 16 cohorts, 331 patients)
N patients per cohort, median (range); number of cohorts with data	25 (10–183); 101	27 (10–107); 15	25 (10–79); 18	29 (16–125); 27	35 (11–183); 22	14 (10–78); 16
N lesions, median (range)	33 (10–171); 13	35 (10–171); 12	NA	NA	NA	NA
Age, in years, mean (range of means of studies)	64 (51–78); 69	61 (51–73); 13	66 (56–76); 12	64 (55–76); 17	62 (59–75); 13	62 (57–78); 13
Gender, male	1791/3270 (54.8%); 74	400/625 (64.0%); 14	209/396 (52.8%); 12	478/966 (49.4%); 21	502/918 (54.7%); 15	128/269 (47.6%); 12
ECOG PS0	614/1251 (49.1%); 29	NA	125/284 (44.0%); 8	340/665 (51.1%); 12	112/241 (46.5%); 5	37/61 (60.7%); 4
Underlying cirrhosis	308/1306 (23.6%); 23	140/449 (31.1%); 9	14/94 (14.9%); 2	82/486 (16.9%); 8	71/261 (27.2%); 3	NA
Previous chemotherapy	734/1671 (43.9%); 44	0/56 (0%); 1	131/247 (53.0%); 6	469/782 (60.0%); 18	91/371 (24.5%); 9	43/180 (23.9%); 10
Previous surgery	738/2008 (36.8%); 43	280/547 (51.2%); 10	12/190 (6.3%); 5	166/726 (22.9%); 16	261/486 (53.7%); 8	19/59 (32.2%); 4
Previous locoregional treatment	137/1001 (13.6%); 25	56/133 (42.1%); 2	12/118 (10.2%); 4	30/425 (7.1%); 10	22/233 (9.4%); 6	4/57 (7.0%); 3
Previous biliary drainage	50/413 (12.1%); 9	NA	21/157 (13.4%); 3	20/196 (10.2%); 4	NA	NA
Largest tumour size in mm, mean (range)	60 (15–115); 38	27 (15–44); 11	58 (43–79); 8	68 (60–77); 5	81 (54–115); 9	94 (83–114); 4
Bilobar disease	712/1186 (60.0%); 25	NA	NA	416/769 (54.1%); 16	197/285 (69.1%); 6	99/132 (75.0%); 3
Multifocal disease	1103/2206 (50%); 44	163/483 (33.7%); 9	78/270 (28.9%); 8	435/696 (62.5%); 11	278/514 (54.1%); 7	137/208 (65.9%); 9
greater than 50% liver involvement	84/610 (13.8%); 15	0/205 (0%); 3	NA	28/260 (10.8%); 8	56/145 (38.6%); 4	NA
Macrovascular Invasion	268/1491 (18.0%); 26	4/448 (0.9%); 8	27/103 (26.2%); 2	129/454 (28.4%); 7	83/421 (19.7%); 5	20/50 (40.0%); 4
Extrahepatic spread	510/2210 (23.1%); 48	10/491 (2.0%); 10	60/188 (31.9%); 5	260/847 (30.7%); 18	142/569 (25.0%); 9	38/115 (33.0%); 6
Visceral metastasis	153/1608 (9.5%); 39	2/474 (0.4%); 9	41/279 (14.7%); 8	66/400 (16.5%); 10	21/328 (6.4%); 5	23/127 (18.1%); 7
Lymph node involvement	409/1871 (21.9%); 41	19/489 (3.9%); 9	120/252 (47.6%); 7	117/400 (29.3%); 10	73/552 (13.2%); 7	49/143 (34.3%); 8

EBRT: external beam radiotherapy, SIRT: selective internal radiation therapy, TACE: transarterial chemo-embolisation, HAI: Hepatic arterial infusion, NA: Not Available.

conventional TACE) was used in 7 of 19 studies, drug-eluting beads in 6, other or mixed in 6. Embolisation was performed without chemotherapy (i.e. transarterial embolisation) in 2 of 22 cohorts, anthracycline single-agent in 3; platinum single-agent in 2, multidrug in 6, mixed regimen in 9. A mean of 3.0 sessions was delivered. Concomitant systemic chemotherapy was delivered in 29 of 39 (74.4%) patients (data only from 2 cohorts). In the HAI group, intra-arterial drugs used were: floxuridine (FUDR) in 2 of 13 cohorts (1 of them being the pooled results of 3 trials), gemcitabine-based in 3, platinum-based in 4, mixed in 4. A mean of 9.3 cycles were delivered (data from 10 cohorts). Concomitant systemic chemotherapy was delivered in 193 of 201 (96.0%) patients (data from 8 cohorts).

Outcomes

Pooled outcomes are presented on Supplementary Table 3, and main results are summarised in Fig. 2.

Forest-plot of meta-analyses of proportions estimating pooled response rates across the different groups are presented in Supplementary Fig. 2. Regarding pooled response rates, every estimate demonstrated significant evidence of heterogeneity, except for complete response rate after ablation.

Ablation was associated with a pooled complete response rate of 93.9%, without evidence of heterogeneity, and with a pooled weighted mean OS of 30.2 months (95% CI: 21.8–38.6). EBRT was associated with a weighted mean 2-year local control rate of 69.1% (95% CI: 48.1–90.2), a pooled weighted mean PFS of 15.6 months (95% CI: 5.4–24.7), and a pooled weighted mean OS of 18.9 months (95% CI: 14.2–23.5). For IAT, pooled response rates were 23.4%, 26.3% and 41.3% for SIRT, TACE and HAI respectively, with strong evidence for heterogeneity within each modality, with pooled weighted mean PFS of 7.8, 15.0 and 10.1 months for SIRT, TACE and HAI respectively, and pooled weighted mean OS ranged were 14.1, 15.9 and 21.3 months for SIRT, TACE and HAI respectively.

The number of studies reporting sub-groups of patients with liver-only disease, patients treated previously with systemic chemotherapy were insufficient to analyse these subgroups, and the number of studies reporting results for patients with first-line and in first-line with systemic treatment could only be pooled when combining all IAT. Results of pooled analysis of IAT are presented in Table 4 and Fig. 3. Pooled weighted mean OS and pooled response rates seemed better in patients treated in first-line with systemic chemotherapy (25.2 months and 52%), when compared to patients treated in first-line, with or without, systemic chemotherapy (20.7 months and 44.2%); and when compared to the overall population (15.7 months and 28.6%). In the former subgroup, there was also less evidence of heterogeneity between studies. Pooled secondary resection rate was 14.0% in patients treated in first-line with concomitant systemic chemotherapy.

Discussion

This systematic review identified extensive literature focusing on the use of LRT for the treatment of patients with iCC. This clearly demonstrates that the patient population exists and is of interest to many research groups worldwide. However, the quality of the studies was overall insufficient to derive strong recommendations (with the exception of consistent good outcomes for ablation). Despite this, the pooled results presented here establish benchmarks to design future clinical trials, which are still needed.

A first goal of this systematic review was to assess whether recommendations could be made based on the current literature (Fig. 4). For ablation, the identified studies demonstrated consistent results, with a non-heterogeneous complete response rate of 93.9%, and a median OS of 30.2 months, results that appear comparable to surgical series (bearing in mind the very different populations included in ablation vs surgical series: smaller tumours, but more frequently represented treatment of recurrence after previous surgery (51.2%) and more

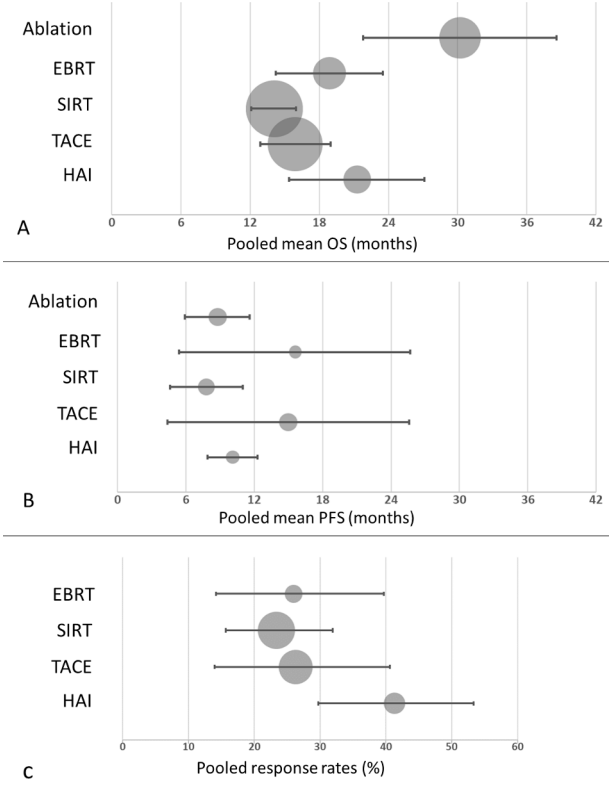

Fig. 2. Main pooled results (EBRT: external beam radiotherapy, SIRT: selective internal radiation therapy, TACE: transarterial chemo-embolisation, HAI: Hepatic arterial infusion).

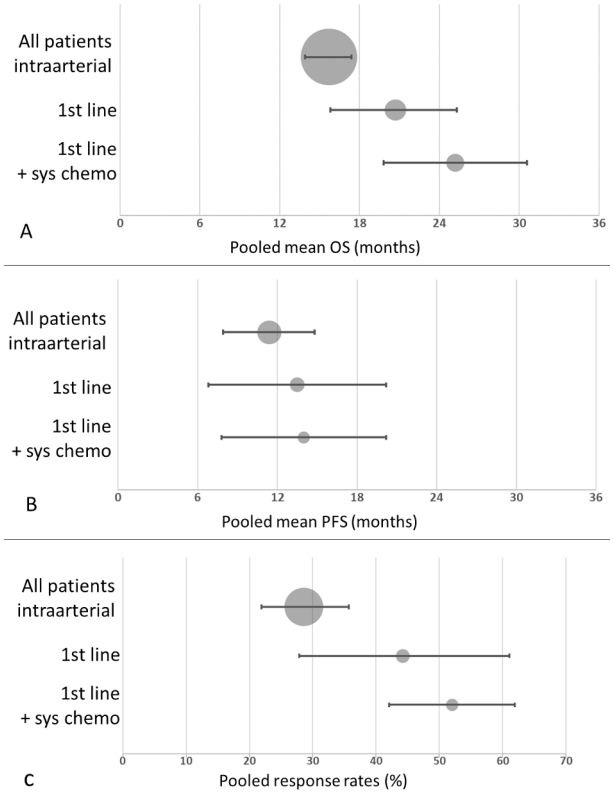

Fig. 3. Main pooled results of intra-arterial therapies, and subgroup analyses.

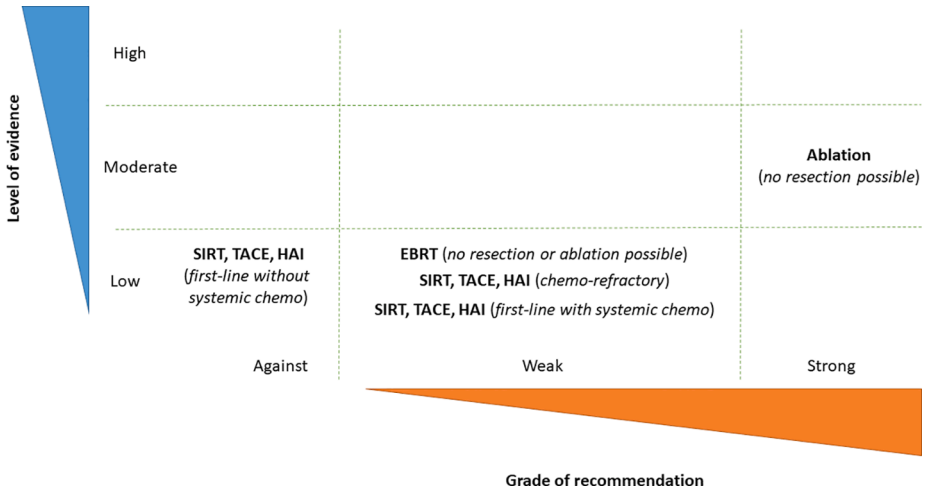

Fig. 4. Proposed recommendations for the current role of loco-regional treatment in the treatment of patients with intrahepatic cholangiocarcinoma.

frequently in a cirrhotic liver (31.1%), due to the inclusion of patients deemed unsuitable candidates for surgery) [11]. Despite the retrospective nature of the data available, the consistency of good outcomes justifies a strong recommendation based on a moderate level of evidence, for patients who are not candidates for resection.

In contrast to ablation, results of EBRT and IAT suffered from high heterogeneity of the results and unclear superiority of outcomes, as compared with what could be expected from systemic chemotherapy in liver-only iCC (pooled objective response rates of 23.4% to 41.3%; and pooled mean OS ranging between 14.1 and 21.3 months with wide CIs). These results do not allow for strong recommendations, especially in the context of the efficacy demonstrated in phase III trials with systemic chemotherapy [3,12]. Comparison of efficacy between the three IAT modalities would prove difficult as the populations included differed. However, based on the subgroup analysis of IAT in the first-line setting with concomitant systemic chemotherapy, and the overall results of IAT that appears promising in contrast to second-line systemic chemotherapy, IAT may be considered in the first-line setting in appropriate circumstances when combined with systemic chemotherapy or in chemo-refractory patients. Moreover, EBRT could be considered in selected cases of unresectability, and when ablation is not feasible.

Importantly, this systematic review should serve as a benchmark for the design of future studies. The results of the only randomised trial included in this systematic review, comparing gemcitabine-cisplatin combined with TACE using irinotecan-loaded drug-eluting beads with gemcitabine-cisplatin alone are promising: there was significantly more downsizing with resection/ablation in the TACE arm (25% vs 8%, P less than 0.005), and improved OS (33.7 vs 12.6 months, $p = 0.048$) [13]. However, the limited number of patients included ($n = 48$) will not be sufficient to derive a strong recommendation. Results of randomised trials for SIRT (SIRCCA randomised phase II trial, clinicaltrials.gov identifier NCT02807181) and for EBRT (ABC-07 randomised phase II trial, ISRCTN identifier 10639376) are awaited, but the early closure of SIRCCA might lead to insufficient power.

Interestingly, different publications reported secondary resection following downsizing with IAT of initially unresectable iCC, evaluated in the pooled analysis as 14.6% of patients treated with systemic chemotherapy in the first-line setting [14–20], with a potential for long-term survival for these patients [21]. Analysis of landmark survival of patients with BTC treated with systemic chemotherapy suggested that patients treated with combination therapy, for iCC and with locally-advanced disease had higher probability of further survival [22]. Another important point to consider in iCC is the need to search for targetable alterations, with promising outcomes presented after targeted treatment for patients with *IDH1* mutations, *FGFR2* fusions or *BRAF* V600 mutations [23].

Most of the studies included were single-centre retrospective studies. Only one randomised controlled study was identified [13], currently published only in abstract form, and thus none of the studies qualified as low risk of bias, and only 15% were considered as intermediate risk of bias (corresponding mostly to well-designed prospective single-arm clinical trials). Moreover, there were important inconsistencies in the reporting of the data. Apart from gender and age, none of the parameters were reported in more than half of the studies. While cirrhosis can be present in iCC and was associated with increased toxicity in a previous trial of SIRT [14], only 23 out of 101 cohorts reported the frequency of cirrhosis in their population. Some parameters representing similar characteristics were reported differently: the extent of the disease was provided either by tumour size, bilobar involvement, multifocality and/or involvement of 50% the liver. Standardized reporting of results of LRT for iCC would be useful, as has been proposed for SIRT [24].

The interpretation of this pooled analysis is limited by the large heterogeneity of the results, illustrated by wide CIs and significant tests for heterogeneity (with the notable exception of complete response rates after ablation). This might be related to the heterogeneity of the population targeted between studies, thus accounting for inter-study heterogeneity. The treatment modalities were studied in different populations. For this reason, results have not been compared between modalities. Also, for each treatment modality, studies varied greatly in the population included. A meta-regression analysis of SIRT studies identified that series including higher proportions of treatment-naïve patients, with mass-forming iCC, and concomitant chemotherapy reported better results [25].

Limitations of the current work are related to the quality of the literature which did not allow for the assessment of all subgroups that was initially planned. Moreover, due to the heterogeneity of reporting, it was not possible to precisely investigate the heterogeneity of the results observed among studies. Publication bias was not assessed as the literature review mostly consisted of retrospective single-arm studies. Moreover, limited information was provided as regards to molecular alterations.

In conclusion, prospective evidence (in particular from randomized controlled trials) for the use of LRT in the treatment of patients with iCC is an area of unmet need. Future research seems justified by the encouraging results presented here. Future phase III clinical trials should be adequately powered to detect clinically relevant differences in survival. An international collaborative effort is necessary to make these trials possible.

Notes

Data sharing

Sharing of the data will be done on request to the corresponding authors.

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CRediT authorship contribution statement

Julien Edeline: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Angela Lamarca:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Resources, Software, Validation, Visualization, Writing – review & editing. **Mairéad G. McNamara:** Conceptualization, Validation, Writing – review & editing. **Timothy Jacobs:** Conceptualization, Software, Validation, Writing – review & editing. **Richard A. Hubner:** Conceptualization, Validation, Writing – review & editing. **Dan Palmer:** Conceptualization, Validation, Writing – review & editing. **Bas Groot Koerkamp:** Conceptualization, Validation, Writing – review & editing. **Philip Johnson:** Conceptualization, Validation, Writing – review & editing. **Boris Guiu:** Conceptualization, Validation, Writing – review & editing. **Juan W. Valle:** Conceptualization, Data curation, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Writing – review & editing.

Declaration of Competing Interest

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctrv.2021.102258.

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