**Systematic review and pooled analysis of locoregional therapies in patients with intrahepatic cholangiocarcinoma**

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**Abstract:**

Background: Locoregional treatments (LRT) including radioembolisation (SIRT), transarterial chemo-embolisation (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 a total of 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, and 19% were only available in abstract form.

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 (all patients) 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. Benchmark outcome estimates are provided to inform the design of phase III trials.

**Lay summary:**

Locoregional treatment has been used to treat patients suffering from intrahepatic cholangiocarcinoma, when it is confined to the liver; however, the literature is not well summarized. In this work, we systematically reviewed all the studies involving locoregional treatment applied to intrahepatic cholangiocarcinoma patients. This literature was heterogeneous, and relies mostly on designs insufficient to derive strong recommendations. However, ablation was associated to good results, and might be used in small tumors when surgery is not possible. This review might also help for the design of future clinical trials.

**Introduction**

Intrahepatic cholangiocarcinoma (iCC) has a rising incidence in Western countries [1]. Due to its relative rarity, treatment strategies of systemic therapies are mostly derived from the results of prospective trials conducted in biliary tract cancers (BTC) of different origins [2,3]. However, iCC might present a different biology, and hence prognosis, compared with other origins of BTC (i.e. perihilar or distal cholangiocarcinoma or gallbladder cancer) [4]. Moreover, locally-advanced and metastatic BTC are frequently pooled in the same studies as advanced BTC. However, outcomes of 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 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 of them do not include all the literature currently available [8–10].

We thus performed a systematic review of the existing literature regarding the use of LRT in patients with iCC. The aims were: firstly, to evaluate the available evidence to determine if recommendations could be developed regarding the role of LRT in the treatment of patients with iCC, and secondly, to provide benchmarks of outcomes for the design of phase III trials, if the literature was insufficient to derive recommendations.

**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 follows 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 then 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 unresectable iCC, 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 resectable or resected tumours, 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 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). Each of these items was scored as low risk of bias, intermediate risk of bias 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 will be collected from articles and pooled overall and for each LRT: study characteristics (prospective vs retrospective, number of patients, existence of a control group), patients demographics, presence of cirrhosis, performance status, previous treatment (chemotherapy, surgery, biliary drainage), extent of the disease (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); 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 (I2 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, the Embase search identified 4637 abstracts, of which 93 entries were finally selected after review of full content (Figure 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 utilised 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 for pooled analyses: 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 figure 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, 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 having a high risk of bias, 14 (15%) as having intermediate risk of bias, and none as having a 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%).

*Description of the cohorts of patients included*

Data provided by individual studies describing the patients’ 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 and patients. There was also heterogeneity between modalities when reporting. The median number of patients per cohorts included was 25, and ranged from 10 to 183 patients. There were differences in the characteristics of the population included between the different treatment modalities, notably regarding the use of previous chemotherapy, previous surgery, tumour size, multifocality of the disease, macrovascular invasion and extrahepatic spread.

*Description of the treatment applied*

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 50Gy (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 (ie, conventional TACE) was used in 7 of 19, drug-eluting beads in 6, other or mixed in 6. Embolisation was performed without chemotherapy 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, floxuridine (FUDR) was used in 2 of 13 cohorts, 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 Table 3, and main results are summarised in Figure 2.

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

Ablation was associated 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-years local control rate was 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 ranged between 23.4% and 41.3%, in every case with strong evidence for heterogeneity within each modality, with pooled weighted mean PFS ranging from 7.8 to 10.1 months, and pooled weighted mean OS ranged from 14.1 to 21.3 months.

The number of studies reporting sub-groups of patients with liver-only disease, patients treated previously with systemic chemotherapy were insufficient to pool, 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 Figure 3. OS and response rates seemed better in patients treated in first-line with systemic chemotherapy, as compared both with patients treated in first-line with or without systemic chemotherapy, and as compared to the overall population. In the former subgroup, there was also less evidence of heterogeneity between studies.

**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, that are still needed.

A first goal of this systematic review was to assess whether recommendations could be made based on the current literature (Figure 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 (95% CI: 21.8-38.6), results that could appear similar to surgical series (bearing in mind the very different populations included in ablation vs surgical series: smaller tumours, but more frequently recurring after previous surgery (51.2%) and more 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 confidence intervals). 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 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 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 to resection/ablation in the TACE arm (25% vs 8%, P<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 phase III trial, clinicaltrials.gov identifier NCT02807181) and for EBRT (ABC-07 phase II trial, ISRCTN identifier 10639376) are awaited, but the early closure of SIRCCA might lead to insufficient power. This systematic review will help to define statistical hypothesis better and help to plan future phase III randomised trials that are still clearly needed.

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 this downsized 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 good 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 is a known risk factor for of 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. Development of consistency in the reporting of results of LRT for iCC would be useful, as was for example previously proposed for SIRT [24].

The interpretation of this pooled analysis is limited by the large heterogeneity of the results, illustrated by wide confidence intervals 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. All treatment modalities are not applied to similar populations, depending on tumour burden. For this reason, results have not been compared between modalities. Also, within a same 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 assessment of all subgroups that were 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 possible to assess 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 for the use of LRT in the treatment of patients with iCC is an area of unmet need, and future research seems justified by the encouraging results presented here. Future phase III clinical trials should be designed based on achievable goals. A collective academic effort is necessary to make these trials possible.

**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

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**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

**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 |
| > 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

**Table 3:** Pooled outcomes of locoregional treatment for patients with intrahepatic cholangiocarcinoma

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Ablation** | **EBRT** | **SIRT** | **TACE** | **HAI** |
| Pooled weighted mean **OS**months (95% CI); number of studies with data available | 30.2 (21.8-38.6); 14 | 18.9 (14.2-23.5); 15 | 14.1 (12.1-16.0); 26 | 15.9 (12.9-19.0); 20 | 21.3 (15.4-27.1); 13 |
| Pooled weighted mean **PFS**months (95% CI) ; number of studies with data available | 8.8 (5.9-11.6); 9 | 15.6 (5.4-25.7); 5 | 7.8 (4.6-11.0); 8 | 15.0 (4.4-25.6); 7 | 10.1 (7.9-12.3); 9 |
| Pooled weighted mean **liver PFS** months (95% CI) ; number of studies with data available | 15.6 (0-140.5); 2 | 4.1 (n/a); 1 | 4.9 (0.8-9.2); 3 | 4.9 (0-43.0); 2 | 8.8 (0-64.0); 2 |
| Pooled **response rate**% (95% CI); heterogeneity I2-p value; number of studies with data available | n/a; n/a; 1 | 26.0 (14.2-39.7); 68.3%-0.004; 7 | 23.4 (15.7-31.9); 85.0%-0.000; 18 | 26.3 (14.0-40.6); 92.8%-0.000; 15 | 41.3 (29.7-53.3); 70.3%-0.000; 13 |
| Pooled **complete response rate** % (95% CI); heterogeneity I2-p value; number of studies with data available | 93.9 (90.9-96.5); 0.0%-0.742; 8 | 5.2 (0-17.7); 70.9%-0.008; 5 | 0.2 (0.0-1.4); 22.1%-0.233; 11 | 0.1 (0-0.1); 32.9%-0.105; 15 | 0.4 (0-3.4); 0.0%-0.925; 8 |
| Pooled **disease control rate**% (95% CI); heterogeneity I2-p value; number of studies with data available | 97.4 (90.4-100); n/a; 2 | 75.5 (53.8-92.4); 79.9%-0.001; 5 | 76.7 (66.3-85.8); 87.2%-0.000; 13 | 82.7 (73.9-90.1); 84.4%-0.000; 15 | 76.8 (68.4-84.4); 27.0%-0.187; 11 |
| Pooled **secondary resection rate**% (95% CI); heterogeneity I2-p value; number of studies with data available | n/a; n/a; 1 | n/a; n/a; 1 | 7.6 (3.7-12.5); 68.4%-0.002; 8 | 12.7 (6.4-20.3); 3.5%-0.375 | 8.3 (3.2-14.9); 23.0%-0.261; 6 |
| Pooled weighted mean **2-year local control rate**% (95% CI); number of studies with data available | 79.3 (0-100); 2 | 69.1 (48.1-90.2); 6 | n/a | n/a | n/a |

Table 4: Outcomes in patients with intrahepatic cholangiocarcinoma for the intra-arterial therapies pooled together, and subgroup analyses

|  |  |  |  |
| --- | --- | --- | --- |
|  | **All intra-arterial therapies combined** | **Subgroup first-line** | **Subgroup first-line and concomitant systemic chemotherapy** |
| **Pooled weighted mean OS****months (95% CI); number of studies with data available** | 15.7(13.9-17.4); 59 | 20.7 (15.8-25.3) ; 14 | 25.2 (19.8-30.6) ; 8 |
| **Pooled weighted mean PFS****months (95% CI) ; number of studies with data available** | 11.4(7.9-14.8); 24 | 13.5 (6.8-20.2) ; 7 | 14.0 (7.8-20.2) ; 7 |
| **Pooled response rate****% (95% CI); heterogeneity I2-p value; number of studies with data available** | 28.6%(21.9-35.7); 88.9%-0.000; 46 | 44.2% (27.9-61.1); 33.7%-0.000 ; 7 | 52% (42.1-61.9) ; 5.8%-0.22 ; 5 |
| **Pooled disease control rate****% (95% CI); heterogeneity I2-p value; number of studies with data available** | 79.2%(73.7-84.3); 81.1%-0.000; 39 | 87.6% (72.0-97.9) ; 24.7%-0.000 ; 6 | 88.2% (72.9-98.3) ; 8.7%-0.034 ; 4 |
| **Pooled secondary resection rate****% (95% CI); heterogeneity I2-p value; number of studies with data available** | 8.6%(5.5-12.1); 52.8%-0.005; 18 | 12.8% (5.7 – 21.8) ; 18.3%-0.005; 7 | 14.0% (5.8% - 24.6%) ; 11.3%-0.024 ; 5 |

**Figure 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)



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



**Figure 3:** Main pooled results of intra-arterial therapies, and subgroup analyses

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**Figure 4:** Proposed recommendations for the current role of loco-regional treatment in the treatment of patients with intrahepatic cholangiocarcinoma

