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Chemotherapy with or without Selective Internal Radiation Therapy for intrahepatic cholangiocarcinoma: data from clinical trials

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Short Title: Chemotherapy +/- SIRT for iCC: metaanalysis

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Julien Edeline consults and received grants from Beigene, Boston Scientific, and Bristol Myers Squibb. He consults for AstraZeneca, Basilea, Bayer, Eisai, Incyte, Ipsen, MSD, Roche, Merck Serono, Servier, and Taiho. He is employed by Amgen. John Bridgewater

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Graphical Abstract

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Abstract

In advanced, liver-only intrahepatic cholangiocarcinoma (iCCA), Selective Internal Radiation Therapy (SIRT) has been suggested as promising in non-randomized studies. We aimed to compare data from patients with advanced, liver-only iCCA treated in first line in clinical trials with either chemotherapy alone or the combination with SIRT. We collected individual patients' data from the ABC-01, ABC-02, ABC-03, BINGO, AMEBICA and MISPHEC prospective trials. Data from patients with liver-only iCCA treated in chemotherapy-only arms of the first five trials were compared with data from patients treated with SIRT and chemotherapy in MISPHEC. Emulated target trial paradigm and Inverse Probability of Treatment Weighting (IPTW methods) using the propensity score were used to minimize biases. We compared 41 patients treated with the combination with 73 patients treated with chemotherapy alone, the main analysis being in 43 patients treated with cisplatin-gemcitabine or gemcitabine-oxaliplatin. After weighting, overall survival was significantly higher in patients treated with SIRT: median 21.7 months [95% Confidence Interval (CI): 14.1; not reached] vs 15.9 months [95%CI: 9.8; 18.9], Hazard Ratio = 0.59 [95%CI: 0.34; 0.99], p=0.049. Progression-free survival was significantly improved: median 14.3 months [95%CI: 7.8; not reached] vs 8.4 months [95%CI: 5.9; 12.1], Hazard Ratio = 0.52 [95% CI: 0.31; 0.89], $p < 0.001$. Results were confirmed in most sensitivity analyses. Conclusion: This analysis derived from prospective clinical trials suggests that SIRT combined with chemotherapy might improve outcomes over chemotherapy alone in patients with advanced, liver-only iCCA. Randomized controlled evidence is needed to confirm these findings.

Introduction

Intrahepatic cholangiocarcinoma (iCCA) is the second most frequent primary liver cancer after hepatocellular carcinoma. Its incidence is rising in Western countries, possibly owing to increase of chronic liver disease and better recognition versus carcinoma of unknown primary or hepatocellular carcinoma (1). While resection is the only curative option, patients frequently present with unresectable disease at diagnosis. In the advanced setting, standard of care treatment is mostly based on data coming from studies that included patients with all types of biliary tract cancers (BTC). The recommended first-line standard of care is currently the cisplatin-gemcitabine combination (CISGEM regimen) based on the results of the ABC-02 trial; recently, the addition of durvalumab to CISGEM demonstrated a survival benefit leading to its approval by the US FDA and EMA (2,3), as the addition of pembrolizumab demonstrated a survival benefit, currently pending approval by regulatory agencies (4), while triplet chemotherapy regimen failed to improve outcomes in studies in Western population (5,6).

iCCA may present as a locally-advanced disease, with liver-only extent. In such cases, loco-regional treatment approaches have been studied during the last decade, but most of the data comes from small, single-center, retrospective studies, and the level of evidence for loco-regional treatments is thus quite low (7). Specifically, Selective Internal Radiation Therapy (SIRT) using Yttrium-90 microspheres (also known as radioembolization) has been studied mostly in retrospective studies. In a recent systematic review, we described heterogeneous results achieved with SIRT, with objective response rates ranging from 0% to 36%, and median Overall Survival (OS) ranging from 8.7 to 32.3 months, mostly coming from retrospective studies (7). This heterogeneity was probably related to the very heterogeneous population in which SIRT was applied (e.g. first-line in combination with chemotherapy vs

chemorefractory; liver-only vs with extra-hepatic disease…). We previously published the results of the multicenter, single-arm MISPHEC trial assessing the combination of SIRT with CISGEM chemotherapy in patients treated in first line for liver-only iCCA (8). Results were promising with a 39% response rate, a 98% disease control rate, a median Progression-Free Survival (PFS) of 14 months and a median OS of 22 months. However, the results of systemic chemotherapy alone in liver-only iCCA might be better, with a median OS of 16.7 months, than those achieved in all-comers BTCs, as suggested by a recent analysis (9) ; however, available data are scarce for this specific subgroup. Cross studies comparison is challenging, specially taking into account that the selection of patients in the MISPHEC trial – liver-only iCCA – might have influenced favorably the outcomes over the patients included in the systemic chemotherapy alone studies. Probably due to the limitations of the current data, recommendations currently diverge regarding the role of SIRT, or more generally loco-regional treatments, for liver-only iCCA, with the ESMO and EASL-ILCA guidelines recently suggesting that loco-regional treatments might be considered an option, while the recent AASLD guidelines stating that data are insufficient to recommend loco-regional treatment as a standard therapy for locally advanced unresectable iCCA (10–12).

We thus planned to compare individual-patient level data of patients treated within MISPHEC with those of patients treated with first-line chemotherapy alone within prospective clinical trials, focusing on the population with liver-only iCCA, using robust methods for matching of population.

Methods

We conducted a retrospective study based on individual patients' data from previous prospective clinical trials: ABC-01/02 (2), ABC-03 (13), BINGO (14), PRODIGE 38

AMEBICA (5) and MISPHEC (8), involving patients treated as first line for an advanced or metastatic BTC. All participants of all trials provided written consent for participating in the clinical trials, which were conducted in accordance with the declaration of Helsinki. The institutional review boards of each previous trial sponsor approved the present study and the use of the data.

We included in our analysis all patients treated in MISPHEC. One inclusion criteria of MISPHEC was no or limited extrahepatic disease (limited extrahepatic disease was defined as hilar lymph node ≤3 cm or <5 lung nodules, each ≤10 mm). As we could not apply retrospectively these size criteria to the patients included in the other trials, we included only patients from the other trials reported to have an iCCA without metastasis.

Description of the previous trials

Briefly, ABC-01 was the randomized phase 2 part of the ABC-02 phase 3 trial comparing CISGEM combination (cisplatin 25 mg/m² and gemcitabine 1000 mg/m² Day 1 and Day 8 repeated every 21 days for 8 cycles) with gemcitabine monotherapy, and both trials combined included 200 patients that received the combination (2). The results were in favor of the combination and set the CISGEM regimen as the standard of care for these patients. ABC-03 was a randomized phase 2 trial comparing the CISGEM combination with or without cediranib (an oral inhibitor of VEGF receptor 1, 2, and 3), and included 124 patients [10]. The results were negative, with no improvement of the primary endpoint, PFS (HR= 0.93, 95% CI: 0.65–1.35; p=0.72), and no difference in OS (HR 0.86, 95% CI: 0.58–1.27, p=0.44), but a greater response rate (RR, 44% vs 19%, p=0.0036). The BINGO trial was a randomized phase 2 trial comparing gemcitabine-oxaliplatin (GEMOX regimen: gemcitabine 1000 mg/m² and oxaliplatin 100 mg/m² given every 2 weeks) with or without cetuximab (an EGFR-targeting monoclonal antibody) and included 150 patients [11]. The trial was negative, with no improvement of the primary endpoint, 4-month PFS rate, and no difference in PFS, OS or RR.

The PRODIGE 38 AMEBICA trial was a planned randomized phase 2/3 trial that compared CISGEM with FOLFIRINOX (oxaliplatin 85 mg/m2, irinotecan 180 mg/m2, folinic acid 400 mg/m2, and fluorouracil 2,400 mg/m2 over 46 hours, every 2 weeks) and included 190 patients [12]. The phase 2 part was negative, showing no improvement in the primary endpoint, 6-month PFS rate, and no difference in PFS, OS and RR. The MISPHEC trial was a single-arm phase 2 trial and tested the combination of CISGEM with SIRT using Yttrium-90 glass microspheres, and included 42 patients (8). Patients received either one (unilobar involvement) or two (bilobar involvement) SIRT doses during cycle 2 or cycle 3 of chemotherapy. The trial was positive, meeting its primary endpoint of RR > 22% with a 39% RR (90% CI, 26%-53%), and showed a 98% disease control rate, a median PFS of 14 months (95%CI, 8-17) and a median OS of 22 months (95%CI, 14-52). The main trials characteristics are summarized in Supplementary table 1.

Emulated target trial

The emulated target trial approach addresses the pitfalls of using retrospective data(15). It allows the implementation a priori of appropriate measures to limit selection, information and confusion bias between compared arms. Furthermore, as SIRT treatment requires a delay between inclusion and treatment delivery to rule out contraindications (e.g. pulmonary shunt), the disease may progress during the period, excluding the most severe patients. This selection bias known as the immortal time bias was limited in the present study by excluding from the analysis all patients in the control arm who died or progressed early, i.e. before the median time necessary to achieve the planning angiography and the treatment in the MISPHEC study (which was 9 days). Supplementary Table 2 lists the key components of our target trial protocol.

The main analysis was performed on the population treated with what are considered standard of care (SOC) first-line chemotherapy (cisplatin-gemcitabine or GEMOX), with two sensitivity analyses in patients treated with all types of experimental chemotherapy (including the use of targeted therapy), or patients treated with CISGEM exclusively.

Statistical analyses

Analyses were performed on full data set after missing data were imputed with multivariable imputation by chained equations using the CART method. Descriptive statistics used means (standard deviations) for continuous variables and reported counts and percentages for categorical variables. Baseline characteristics were compared between systemic chemotherapy and systemic chemotherapy + SIRT with Wilcoxon rank-sum tests and Fisher's exact tests. The Kaplan Meier estimator was used to estimate OS and PFS times and Log-Rank tests to compare survival curves. A p value <0.05 was considered as statistically significant.

To take into account absence of randomization for treatment assignment in our study, the inverse probability treatment weighting (IPTW) using a propensity score was implemented to balance observed confounding factors between groups [6]. Propensity scores were obtained using logistic regression model, with treatment group regressed on demographic, liver function and cancer-related variables (gender, age, previous surgery, performance status, total bilirubin, aspartate aminotransferase, alanine aminotransferase, CA19.9 marker). Manual selection of variables and interactions were used to obtain the final model which minimize bias factors' imbalance between groups. Standardized mean differences and variance-ratio were used to compare balance between groups. Stabilized weights were then applied to compute endpoint estimators [7]. Cox proportional models was used to estimate hazard ratios (HR) and their 95% confidence intervals. Proportional risk assumption was tested using

Schoenfeld residuals. Moreover, adjusted and unadjusted best overall responses are presented. A logistic regression is performed in order to estimate odds ratios (OR) and their 95% confidence interval.

Analyses were repeated using the same approach on the only-complete dataset (without missing data imputation) and using another approach based on sample matching with a caliper. Caliper's size is calculated as 0.55 times the standard deviation of the logit of the propensity score [18].

Concerning unmeasured residual confounding factors, the expected value (e-value) which represents the minimal strength of association that a potential confounding factor needs to have to fully explain away the treatment-outcome association we observed, was calculated [8]. Thus, the robustness of our results can be assessed on the basis of the implausible assumption of observing such drastic confounder.

Analyses, results and figures were performed with The R Statistical Computing Environment (R Foundation for Statistical Computing, Vienna, Austria).

Results

Populations included

From the 664 patients included in ABC-01, -02, -03, BINGO, and PRODIGE 38 AMEBICA trials, 75 (11%) were recorded as having liver-only iCCA (Figure 1). Two other patients were excluded for censorship of immortal time bias (one patient) or failure to respect the MISPHEC inclusion criteria (elevated bilirubin, one patient). The main population (comparison of SOC chemotherapy regimen vs SIRT) included 84 patients, while the sensitivity analysis of patients treated with all chemotherapy regimens included 114 patients, and the sensitivity analysis of patients treated with CISGEM included 73 patients.

The baseline characteristics of the patients are reported on Table 1. Overall, all variables except treatment received were evenly distributed between treatment groups. The characteristics of the population included after imputation of missing data are reported on Supplementary Table 3.

Propensity score matching

A propensity score was performed using the IPTW method before survival assessment. After adjustment with IPTW, the propensity score of the 2 groups were comparable (Supplementary Figure 1). Sensitivity analyses were also carried out using IPTW in the dataset without data imputation, and with a propensity score using the caliper method.

Survival estimation in the main population using IPTW

Censored patients have a follow-up median of 24.8 months for patients treated with SIRT vs 15.7 months for patients treated with systemic chemotherapy only. OS was significantly improved in both the unadjusted and adjusted analyses (Figure 2A). In adjusted OS analyses, median OS was 21.7 months [95% Confidence Interval (CI): 14.1; NR] for patients treated with SIRT and systemic chemotherapy vs 15.9 months [95% CI: 9.8; 18.9] for patients treated with systemic chemotherapy only. OS at 12 and 24 months were 77% [95% CI: 59; 87] and 41% [95% CI: 25; 55] with SIRT and systemic chemotherapy vs 59% [95% CI: 42; 73] and 32% [95% CI: 17; 47] with systemic chemotherapy only, respectively.

PFS was significantly improved in both the unadjusted and adjusted analyses (Figure 2B). In adjusted PFS analyses, median PFS was 14.3 months [95% CI: 7.8; NR] for patients treated with SIRT vs 8.4 months [95% CI: 5.9; 12.1] for patients treated with systemic chemotherapy

only. PFS at 12 and 24 months were 54% [95% CI: 37; 69] and 38% [95% CI: 23; 54] with SIRT and systemic chemotherapy vs 37% [95%CI: 22; 52] and 14% [95%CI: 3; 34] with systemic chemotherapy only, respectively. Hazard ratios and E-values are reported on Table 2.

Similar results were achieved using IPTW in the dataset without data imputation (Supplementary Figure 2A and 2B), and when using the caliper method for calculation of the sensitivity score (Supplementary Figure 2C and 2D), with the exception of a non-significant difference in OS when using the caliper method.

Best overall response is reported on Table 3. Unadjusted and adjusted odd ratios for response were 0.85 (95% CI: 0.35; 2.08, p=0.737) and 0.79 (95% CI: 0.32; 1.92, p=0.607), respectively. There were 22% of secondary resections for patients treated with SIRT and systemic chemotherapy vs 7% for patients treated with systemic chemotherapy only (p=0.062). After adjustment with weights, there were 8% of secondary resections for SIRT-treated patients vs 3% for patients treated with systemic chemotherapy only (p=0.113). Unadjusted and adjusted odd ratios for secondary resection were 3.87 (95%CI: 1.04; 18.98, p=0.063), and 2.85 (95%CI: 0.76; 13.33, p=0.143), respectively.

Sensitivity analyses in other populations

We performed a first sensitivity analysis in all eligible patients whatever the chemotherapy regimen received. Results were similar, with an adjusted median OS of 21.7 months [95% CI: 14.3; NR] vs 15.3 months [95% CI: 11.6; 17.7], p<0.01 (Figure 3A and 3B, Table 2 and Supplementary Table 2).

We performed a second sensitivity analysis in patients treated with CISGEM. Results were similar, with an adjusted median OS of 21.7 months [95% CI: 14.3; NR] vs 15.9 months [95% CI: 9.8; 20.2], p<0.01 (Figure 3C and 3D, Table 2 and Supplementary Table 2).

Discussion

We present the first comparison of systemic chemotherapy with or without SIRT in patients with liver-only iCCA. The results suggest improved OS and PFS in patients who received SIRT in combination with systemic chemotherapy. To provide such results, we retrospectively analyzed high-quality individual data from separate previous prospective clinical trials. To limit bias from non-randomized groups comparison, we applied a robust strategy from causal inference in observational studies combining target trial design and IPTW with propensity score to provide adjusted estimates of SIRT impact. We conducted sensitivity analyses with several missing data handling and population selection procedures which all point in the same direction with consistent results. Finally, robustness of the significant and positive associations between survival outcomes and treatment by SIRT and systemic chemotherapy + chemotherapy was confirmed even in presence of residual confounders by high E-values.

This analysis provides novel evidence regarding the potential role of SIRT in liver-only iCCA. Indeed, current guidelines diverge regarding the role of SIRT: the EASL-ILCA guidelines state that intra-arterial therapies may be a reasonable alternative in selected patients with unresectable disease (11); the ESMO guidelines place them only after providing standard-of-care systemic treatment (10) and finally the AASLD guidelines consider the current data insufficient to make a recommendation (12). This might be due to the current absence of comparative data, and the heterogeneity of results presented in retrospective series

(7). Prolonged median OS was seen in the MISPHEC trial, however the results that could be achieved with systemic chemotherapy alone in this selected population of liver-only iCCA were difficult to put into context. A previous analysis of the ABC-01, -02 and -03 trials suggested that OS of this subgroup of patients was better than OS from BTC all-comers (9). We expanded the analysis with an inclusion of more patients (by including additional clinical trials). We confirmed that the achieved median OS (15.3 months) in the population adjusted with the population of the MISPHEC trial seems to be numerically higher that what is expected in BTC all-comers (median OS ranging from 11.0 to 14.1 months in the different arms of the included trials).

The suggested superiority of SIRT combined with systemic chemotherapy over systemic chemotherapy alone needs to be confirmed in a randomized controlled trial. The SIRCCA trial (clinicaltrials.gov identifier NCT02807181), the only phase 3 trial to date that tried to compare SIRT to CISGEM, did not use concomitant chemotherapy with SIRT. Unfortunately, the accrual was stopped prematurely, and the trial might eventually lack power to answer this question. We hope that our analysis might encourage the design of new clinical trials able to answer this important question. Also, the combination of SIRT with other systemic chemotherapy regimens, such as the nab-paclitaxel-cisplatin-gemcitabine triplet who did not improved OS in the phase III SWOG1815 trial but was associated with a trend for improved response rate, might need to be tested prospectively (6,16). Another interesting question might be the combination of SIRT with systemic chemotherapy and anti-PD-(L)1 antibodies, as the TOPAZ-1 study recently showed improved results with the addition of durvalumab to CISGEM (3), which were recently confirmed with the positive results in OS with the addition of pembrolizumab to CISGEM in the Keynote-966 study (4). There is a rationale for combining SIRT with immunotherapy, as the radiation might have immunosensitizing properties, and such combination is an area of interest in other cancers, such as hepatocellular

carcinoma (17). Albeit rare, an abscopal effect has been described in patients treated with SIRT and immunotherapy for metastases from breast cancer (18). Finally, an important development in iCCA is the availability of targeted therapies for a significant population, with positive or encouraging data in case of *FGFR2* rearrangement, *IDH1* mutations, *BRAF* V600 mutations or *HER2* amplifications (19). There is currently no data on potential differential effect of SIRT depending on molecular alterations. Some drugs/alterations have been associated with high response rates (*FGFR2, BRAF, HER2*), and thus the relative priority between SIRT and targeted therapy is questionable. MISPHEC data positions SIRT as a first-line treatment, concomitantly with chemotherapy; data on first-line use of targeted therapy is currently lacking, and the phase III trials of *FGFR* inhibitors are experiencing difficulties of accrual. Moreover, SIRT will remain an option in patients whose tumors have no targetable alterations, which still represent the majority of patients with iCCA.

One specific factor that might trigger positive results with SIRT is the number of patients that could be downsized to surgery. The number of patients downsized to surgery using systemic chemotherapy is not well documented in the literature (20). Using data from prospective clinical trials, we found that only 4% of patients with liver-only iCCA were able to have a resection following systemic chemotherapy, while it was 22% in the SIRT group, but the difference was not statistically significant, and tended to decrease after propensity score matching. We previously showed that outcomes of patients whose tumors have been resected after SIRT tended to be better than outcomes of patients that could be resected upfront (21). This emphasizes the potential major role of loco-regional treatments, especially in patients with unilobar disease whose tumors cannot be resected due to vascular involvement. A strategy to study SIRT in a neoadjuvant approach in resectable iCCA is currently investigated within the SIROCHO trial (ClinicalTrials.gov Identifier: NCT05265208) (22).

Baseline characteristics were evenly balanced between trials, as regards to major prognostic factors (performance status, liver function tests), and target trial eligibility and matching was achieved, enabling to have comparable populations. However, we were not able to take into account tumor burden in the liver (number of lesions, unilobar involvement…), as these data were not recorded in the trials of systemic chemotherapy. We cannot rule out that some selection bias is still present, with lower burden of disease in patients included in the MISPHEC trial as compared to the other trials. Tumor burden might have prognostic implication in liver-only iCCA (albeit this has never been specifically studied, to the best of our knowledge), and thus could bias the results presented here in favor of increased benefit from SIRT. Conversely, we included in the analysis some patients included in MISPHEC with limited extra-hepatic disease (hilar lymph node ≤3 cm or <5 lung nodules, each ≤10 mm) while no such patients were included from the other trials; this might have led to a bias in the opposite direction. FDG-PET might play a role in identifying extra-hepatic disease, and is considered an option for better staging; it might be especially important in patients for which discussion of subsequent surgery is possible (10–12). However, it was not included in the mandatory procedures of any of the trials included.

Our study has some limitations. First, even if the number of patients originally included in the trials was high, the final number of patients with liver-only iCCA was relatively small. However, these figures underline the likely difficulties to complete randomized trials for this rare patient subgroup. Second, the systemic therapy regimens studied were heterogeneous. However, as the results from the initial trials were similar between all arms used in this analysis, pooling the data seems valid, and the results from the sensitivity analyses restricting to CISGEM or expanding to various chemotherapy regimen were consistent with the main analysis. Third, the results were not compared with the results of CISGEM-anti-PD-(L)1 combination. Fourth, we could not exclude the presence of residual confounders that could

not be balanced between arms and could bias our estimates; for example, we do not have data on molecular alterations, which might have a prognostic impact. However, the sensitivity analyses and e-values make the positive association very plausible. Fifth, evaluation of PFS might be hampered by artefacts in patients treated with SIRT, with a possible delay in confirming progression; however, as the effect was seen on both PFS and OS in our analysis, it is unlikely that the effect on PFS is mainly driven by difficulties of radiological evaluation. Finally, some patients were excluded from the MISPHEC trial during the screening procedures, notably for metastases or inadequate general conditions or liver function; we cannot know whether these exclusions resulted from delaying of treatment due to the screening procedures or from better staging; these patients were not followed-up, and we were not able to present an intent-to-treat analysis for all patients. This bia s may have been partially mitigated by our efforts to reduce the immortality time bias.

Conclusion

This analysis suggests that first-line treatment with SIRT and systemic chemotherapy could improve OS over systemic chemotherapy alone in patients with liver-only iCCA. Prospective randomized trials are warranted to confirm these results.

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Figure 1: Study flowchart. iCCA: intrahepatic cholangiocarcinoma; SIRT: Selective Internal Radiation Therapy; CISGEM: cisplatin-gemcitabine combination; GEMOX: gemcitabine-oxaliplatin combination

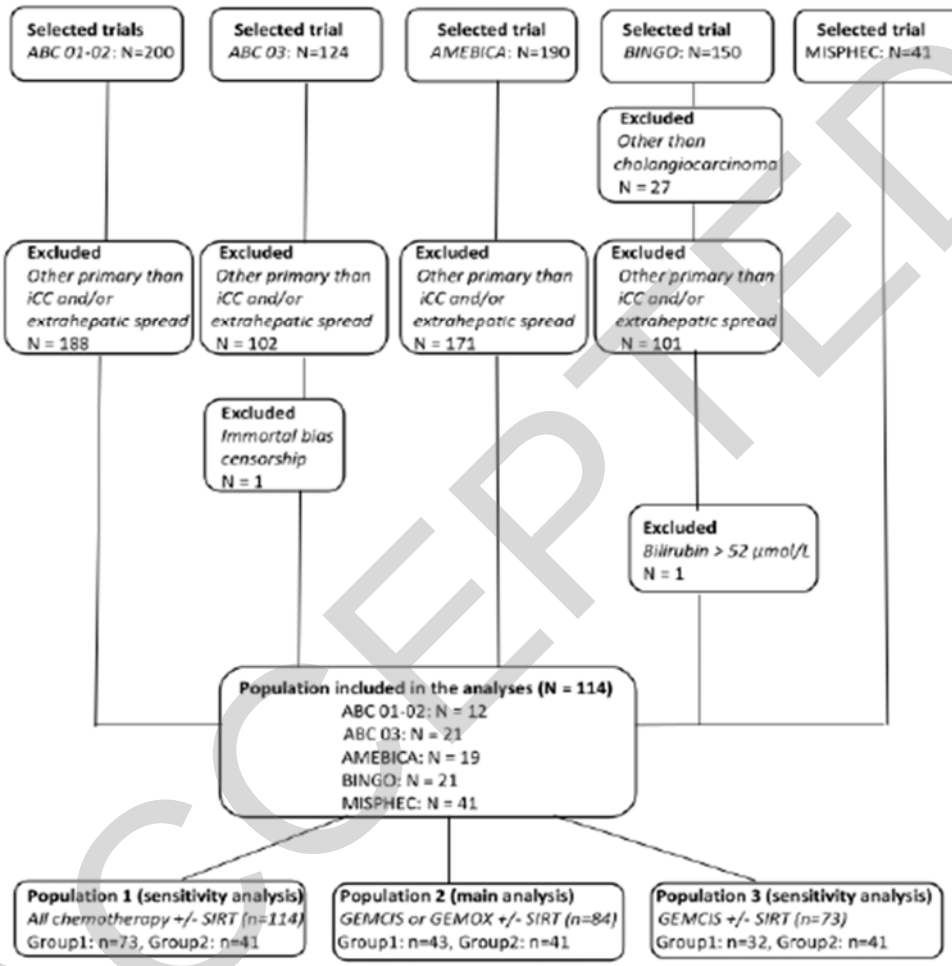


Figure 2A: Unadjusted (dashed lines) and adjusted (full lines) overall survival in patients treated with systemic chemotherapy (blue) vs systemic chemotherapy and SIRT (red).

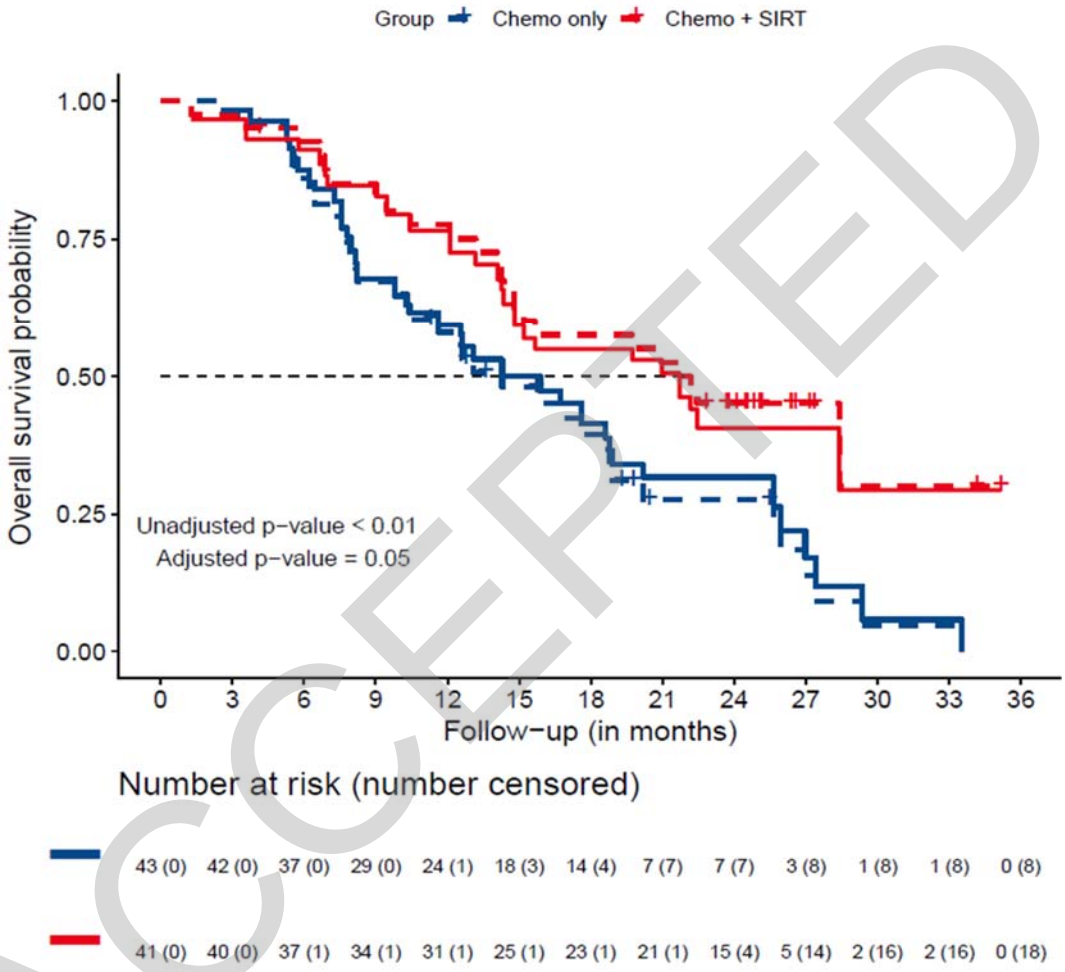


Figure 2B: Unadjusted (dashed lines) and adjusted (full lines) progression-free survival in patients treated with systemic chemotherapy (blue) vs systemic chemotherapy and SIRT (red).

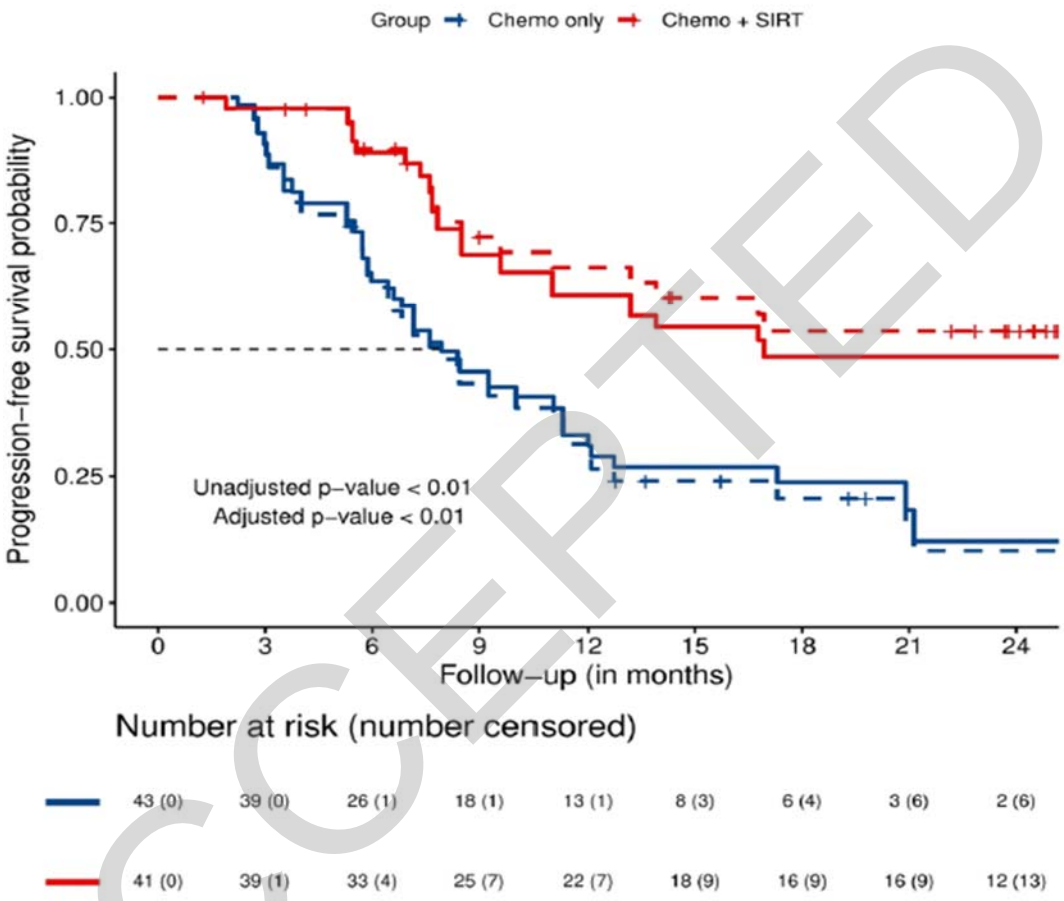
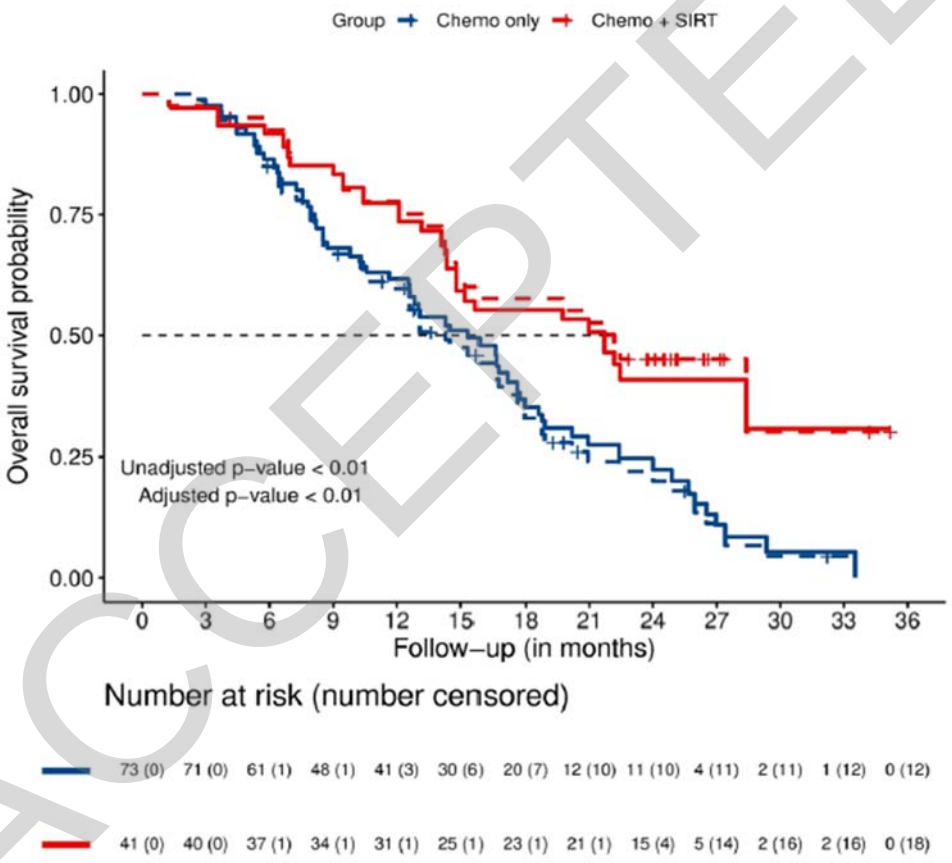
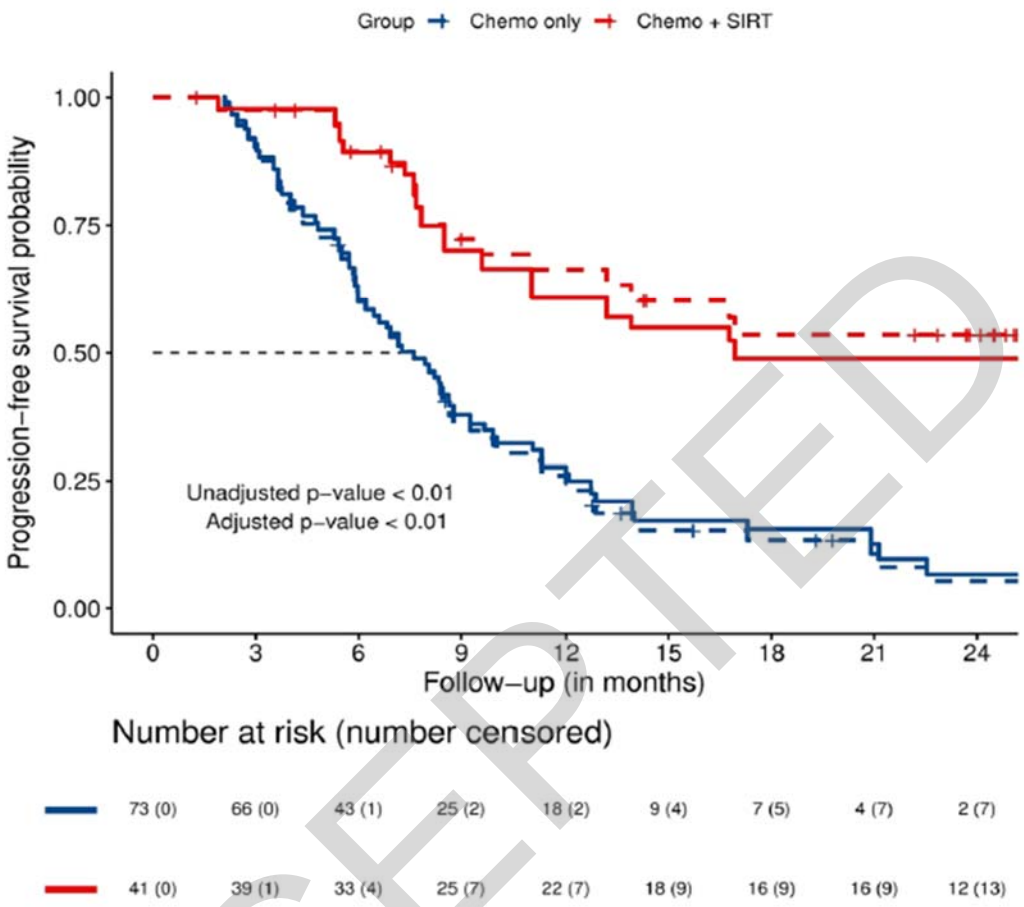
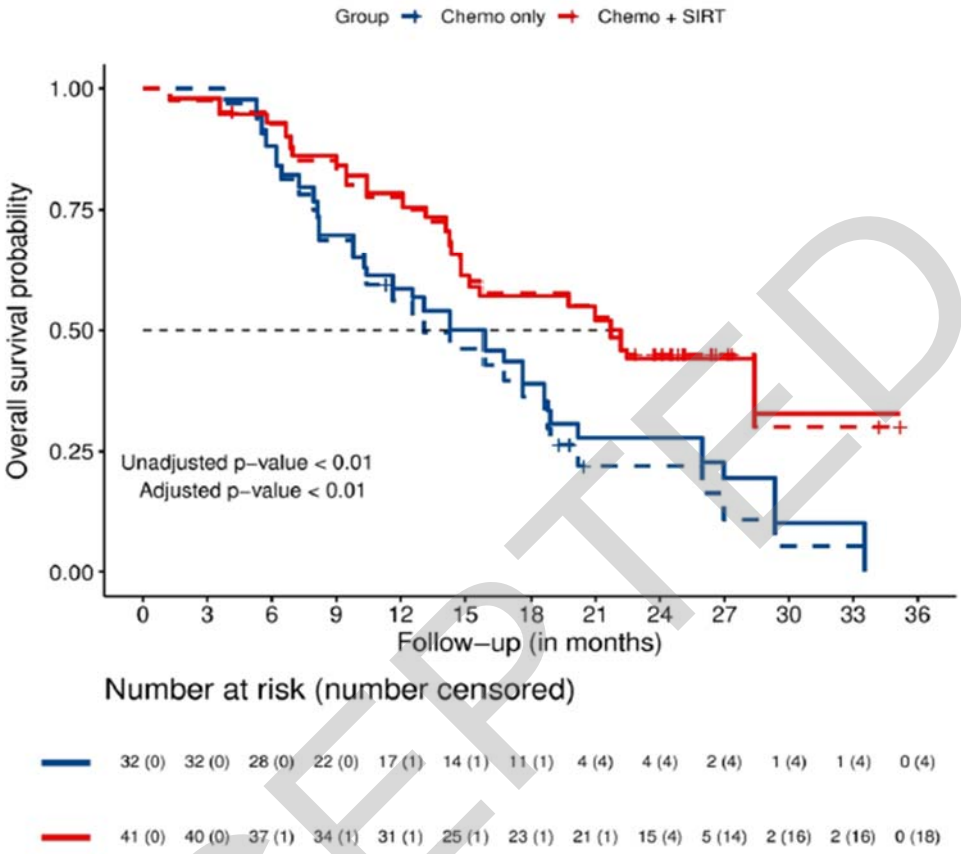


Figure 3: Sensitivity analysis: Unadjusted (dashed lines) and adjusted (full lines) overall survival (A) and progression-free survival (B) in all eligible patients treated with systemic chemotherapy alone (whatever the regimen) (blue) vs systemic chemotherapy and SIRT (red). Unadjusted (dashed lines) and adjusted (full lines) overall survival (C) and progression-free survival (D) in patients treated with CISGEM systemic chemotherapy (blue) vs systemic chemotherapy and SIRT (red).







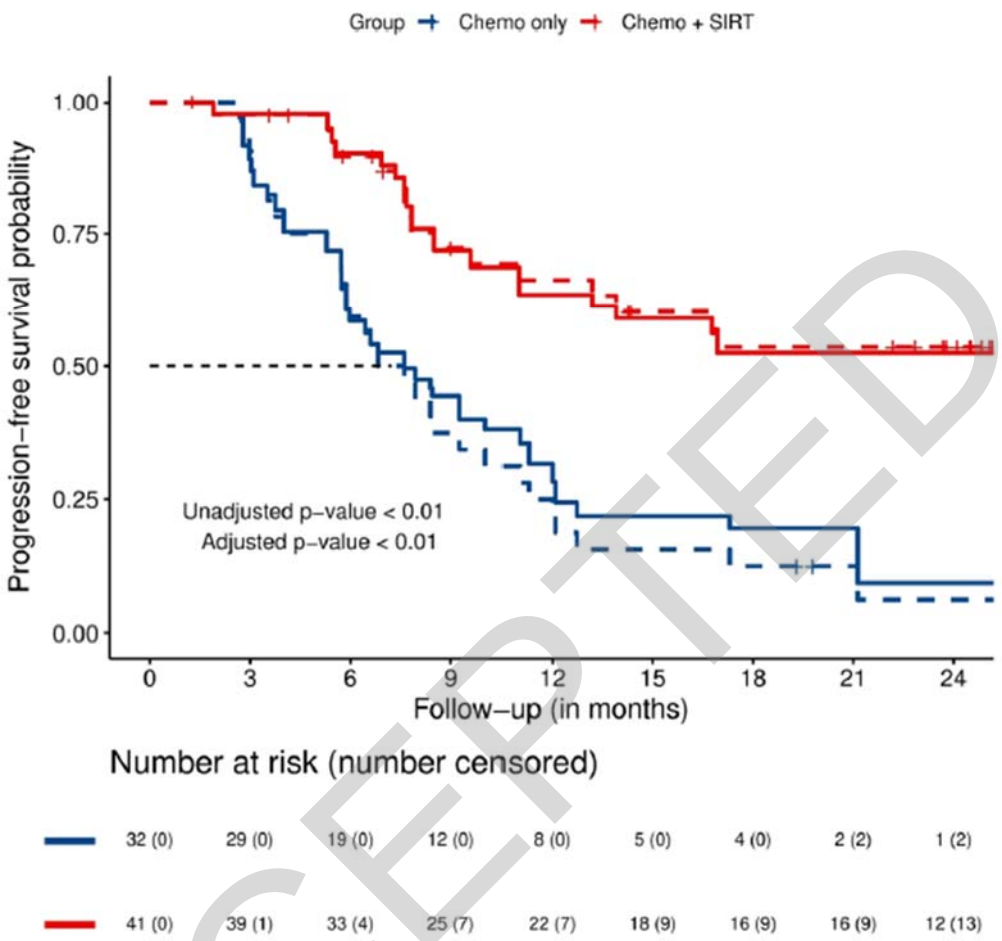


Table 1: Baseline characteristics of the main study population, before imputation of missing data.

Variable	**Overall**, N = 84[1]	**Group 1**, N = 43[1]	**Group 2**, N = 41[1]	**p-value**[2]
Sex				0.825
Female	33 (39%)	17 (40%)	15 (37%)	
Male	52 (61%)	26 (60%)	26 (63%)	
Age	62 (56, 71)	61 (55, 68)	67 (56, 72)	0.397
ECOG Performance status				0.184
0	47 (56%)	21 (49%)	26 (65%)	
1	37 (44%)	22 (51%)	14 (35%)	
Unknown	1	0	1	
Primary tumor site				
iCCA	85 (100%)	43 (100%)	41 (100%)	
Chemotherapy regimen				<0.001
CISGEM	74 (87%)	32 (74%)	41 (100%)	
GEMOX	11 (13%)	11 (26%)	0 (0%)	
SIRT	42 (49%)	0 (0%)	41 (100%)	<0.001

Prior surgery	12 (14%)	7 (17%)	5 (12%)	0.756
Unknown	1	1	0	
Lab results				
Total bilirubin (µmol/L)	13 (9, 19)	12 (8, 17)	13 (10, 19)	0.392
Unknown	5	5	0	
Alanine aminotransferase	28 (21, 47)	32 (21, 55)	28 (21, 41)	0.533
Unknown	7	7	0	
Aspartate aminotransferase	40 (26, 53)	40 (24, 59)	36 (27, 51)	0.932
Unknown	6	6	0	
CA19.9	62 (13, 292)	98 (12, 503)	52 (16, 172)	0.232
Unknown	9	8	1	

[1] n (%); Median (IQR)

[2] Fisher's exact test; Wilcoxon rank sum test

SIRT: Selective internal radiation therapy.

Table 2: Adjusted hazard ratios of overall survival or progression-free survival in the three populations. [1] E-value assesses the minimum strength of association that a potential unmeasured confounder would need to have with both treatment and outcome to fully nullify the specific treatment-outcome association observed.

Study population	Hazard ratio	p-value	E-Value[1]
CISGEM + SIRT vs CISGEM or GEMOX (population 2)			
OS	0.59 [0.34; 0.99]	p=0.049	2.24
PFS	0.52 [0.31; 0.89]	p=0.016	2.52
CISGEM + SIRT vs all chemotherapy regimens (population 1)			
OS	0.52 [0.32; 0.86]	p=0.011	2.52
PFS	0.43 [0.26; 0.70]	p<0.001	2.97
CISGEM + SIRT vs CISGEM (population 3)			
OS	0.52 [0.29; 0.94]	p=0.031	2.52
PFS	0.45 [0.25; 0.81]	p=0.008	2.86

Table 3: Response rates in the main population (CISGEM + SIRT vs GEMOX or CISGEM).

Variable	Overall, N = 84[1]	Group 1, N = 43[1]	Group 2, N = 41[1]	p-value[2]
Unadjusted best response				0.034
Complete response	2 (2%)	2 (5%)	0 (0%)	
Partial response	35 (42%)	19 (44%)	16 (39%)	
Stable disease	40 (48%)	16 (37%)	24 (59%)	
Progression disease	4 (5%)	4 (9%)	0 (0%)	
Unknown	3	2	1	
Adjusted best response				0.030
Complete response	2.05 (3%)	2.05 (5%)	0 (0%)	
Partial response	34.34 (41%)	18.04 (42%)	16.30 (40%)	
Stable disease	38.45 (46%)	15.78 (37%)	22.67 (56%)	
Progression disease	5.27 (6%)	5.27 (12%)	0 (0%)	
Unknown	3	2	1	

[1]n (%); [2]Fisher's exact test.