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Radioembolization Plus Chemotherapy for First-line Treatment of Locally Advanced Intrahepatic Cholangiocarcinoma
A Phase 2 Clinical Trial

Julien Edeline, MD, PhD; Yann Touchefeu, MD; Boris Guiu, MD, PhD; Olivier Farge, MD, PhD; David Tougeron, MD, PhD; Isabelle Baumgaertner, MD; Ahmet Ayav, MD, PhD; Boris Campillo-Gimenez, MD, PhD; Luc Beuzit, MD; Marc Pracht, MD; Astrid Lièvre, MD, PhD; Samuel Le Sourd, MD; Karim Boudjema, MD, PhD; Yan Rolland, MD; Eveline Boucher, MD, PhD; Etienne Garin, MD, PhD

IMPORTANCE Patients with unresectable intrahepatic cholangiocarcinoma (ICC) have a poor prognosis. Selective internal radiotherapy (SIRT) is a promising treatment option for hepatic tumors, but no prospective studies of combination SIRT with chemotherapy have been published to our knowledge.

OBJECTIVE To determine the response rate after SIRT combined with chemotherapy in patients with unresectable ICC.

DESIGN, SETTING, AND PARTICIPANTS This phase 2 clinical trial, the Yttrium-90 Microspheres in Cholangiocarcinoma (MISPHEC) trial, included patients with unresectable ICC who have never received chemotherapy or intra-arterial therapy and were treated at 7 centers which had experience with SIRT between November 12, 2013, and June 21, 2016. Statistical analysis was performed from March 31, 2017, to June 17, 2019.

INTERVENTIONS Concomitant first-line chemotherapy with cisplatin, 25 mg/m^2, and gemcitabine, 1000 mg/m^2 (gemcitabine reduced to 300 mg/m^2 for the cycles just before and after SIRT), on days 1 and 8 of a 21-day cycle for 8 cycles. Selective internal radiotherapy was administered during cycle 1 (1 hemiliver disease) or cycles 1 and 3 (disease involving both hemilivers) using glass Y^{90} microspheres.

MAIN OUTCOMES AND MEASURES Response rate at 3 months according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1. Secondary end points were toxic effects, progression-free survival, overall survival, disease control rate, and response rate according to Choi criteria.

RESULTS Of 41 patients included in the study, 26 (63%) were male, with a mean (SD) age of 64.0 (10.7) years. Response rate according to RECIST was 39% (90% CI, 26%-53%) at 3 months according to local review and was confirmed at 41% as best response by central review; disease control rate was 98%. According to Choi criteria, the response rate was 93%. After a median follow-up of 36 months (95% CI, 26-52 months), median progression-free survival was 14 months (95% CI, 8-17 months), with progression-free survival rates of 55% at 12 months and 30% at 24 months. Median overall survival was 22 months (95% CI, 14-52 months), with overall survival rates of 75% at 12 months and 45% at 24 months. Of 41 patients, 29 (71%) had grades 3 to 4 toxic effects; 9 patients (22%) could be downstaged to surgical intervention, with 8 (20%) achieving R0 (microscopic-free margins) surgical resection. After a median of 46 months (95% CI, 31 months to not reached) after surgery, median relapse-free survival was not reached among patients who underwent resection.

CONCLUSIONS AND RELEVANCE Combination chemotherapy and SIRT had antitumor activity as first-line treatment of unresectable ICC, and a significant proportion of patients were downstaged to surgical intervention. A phase 3 trial is ongoing.

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Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Julien Edeline, Medical Oncology, Centre Eugène Marquis, Av Bataille Flandres-Dunkerque, Rennes 35042, France (j.edeline@rennes.unicancer.fr).

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The incidence of intrahepatic cholangiocarcinoma (ICC) has been increasing in Western countries.[1,2] For advanced ICC, doublet chemotherapy with cisplatin and gemcitabine became the standard treatment after the ABC-02 trial reported a median overall survival (OS) of 11.7 months (confirmed by a meta-analysis).[3-5] However, results in the patient population with locally advanced ICC are less well described. Therapeutic improvements in ICC are necessary.

Radioembolization using yttrium-90 (^{90}Y)-labeled microspheres, also known as selective internal radiotherapy (SIRT), is applied as a locoregional treatment for liver malignancies for both primary tumors and hepatic metastases. Radiolabeled microspheres are administrated via the hepatic arteries, delivering radiotherapy when reaching the tumor vasculature. Multiple single-center series reported results of SIRT among patients with locally advanced ICC[6-19]; however, the largest study published to date included only 85 patients.[18] Results of these studies[6-19] are heterogeneous, with median response rates (RRs) ranging from 5% to 36% and median OS from 9 to 22 months, reflecting the heterogeneity of the population included. A previous study[8] suggested that with first-line treatment, concomitant chemotherapy and SIRT might provide additional benefit, with a median progression-free survival (PFS) of 21.7 months with concomitant chemotherapy vs 13.4 months when chemotherapy was performed before SIRT. Based on these results, we designed a prospective multicenter, single-arm phase 2 trial to assess the effectiveness and safety of SIRT combined with chemotherapy in first-line treatment of unresectable, locally advanced ICC.

Key Points

Question Is selective internal radiotherapy associated with improved response rate in patients with unresectable intrahepatic cholangiocarcinoma?

Findings In this phase 2 clinical trial that included 41 patients, selective internal radiotherapy combined with chemotherapy was associated with an increased response rate of 39%, and 22% of patients were downstaged to surgical intervention. Median progression-free survival was 14 months, and median overall survival was 22 months.

Meaning The findings suggest that selective internal radiotherapy can be considered as a treatment option for the downstaging of patients with unresectable intrahepatic cholangiocarcinoma.

Methods

Study Design and Population

The Yttrium-90 Microspheres in Cholangiocarcinoma (MISPHEC) trial was designed as a first-line multicenter, open-label, single-arm phase 2 clinical trial. The trial was conducted in 7 centers in France from November 12, 2013, through June 21, 2016. The trial was approved by Comité de protection des personnes Ouest V ethics committee, Rennes, France, and was conducted according to Good Clinical Practice and the Declaration of Helsinki.[20] All participants provided written informed consent before inclusion in the trial.

Eligible patients were aged 18 years or older, had unresectable ICC, a measurable lesion (≥2 cm), either noncirrhotic liver or cirrhosis with Child-Pugh score less than B8 (a score of liver function in which lower scores indicate better liver function), Eastern Cooperative Oncology Group performance status of 0 or 1, no or limited extrahepatic disease (limited extrahepatic disease was defined as hilar lymph node ≤3 cm or <5 lung nodules, each ≤10 mm), adequate hematologic or kidney function, albumin level of at least 28 g/L (to convert to milligrams per deciliter, divide by 10), and bilirubin level less than or equal to 3 times the upper limit of normal. Patients who had undergone resection and experienced intrahepatic unresectable recurrence could be included in the study. Unresectability was defined as the inability to resect the cancer with negative margins, leaving 2 adjacent segments of liver with intact portal venous and hepatic arterial inflow and intact biliary and hepatic venous outflow with the future liver remnant of sufficient volume to avoid postoperative liver insufficiency. Evaluation of unresectability was done locally by multidisciplinary team discussion involving hepatobiliary surgeons. Noninclusion criteria were extrahepatic cholangiocarcinoma, gallbladder cancer, pancreatic or ampullary cancer, portal vein thrombosis involving the trunk, previous chemotherapy, intra-arterial or radiotherapy for ICC, or contraindication to either gemcitabine or cisplatin. Patients were excluded if a contraindication appeared during workup angiography, such as lung shunting (lung dose >30 Gy for a single treatment or >50 Gy cumulative [to convert to rads, multiply by 10]), or nonmanageable extrahepatic deposition of technetium Tc 99m macroaggregated albumin on scintigraphy performed after planning angiography.

Procedures

After inclusion, patients initiated chemotherapy with the gemcitabine plus cisplatin regimen. In case of 1 hemiliver involvement, the SIRT was performed during cycle 1 (days 3-21); in case of involvement of both hemilivers, a first SIRT was performed as described previously and a second SIRT procedure was done during cycle 3 (days 3-21) to cover both hemilivers. In case of anatomic variants of liver arteries, up to 3 SIRT sessions were allowed at the discretion of the interventional radiologists (including B.G. and Y.R.). Chemotherapy was continued for a recommended number of 6 cycles, but prolongation of chemotherapy (biweekly gemcitabine plus cisplatin or gemcitabine alone) was accepted when deemed to be necessary by the investigators (including J.E., Y.T., D.T., I.B., M.P., S.L.S., A.L., and E.B.). The gemcitabine plus cisplatin regimen consisted of cisplatin, 25 mg/m^2, administered on days 1 and 8 and gemcitabine, 1000 mg/m^2, administered on days 1 and 8, with cycles repeated every 3 weeks. For the cycle concomitant and the cycle after SIRT, the gemcitabine dose was decreased to 300 mg/m^2 because of concerns about potential toxic effects from the combination with SIRT.

The SIRT procedure was performed as previously described.[21] Percentage of pulmonary shunting and absence of digestive uptake were assessed after ^{99m}Tc macroaggregated albumin was injected (185 MBq) during a first angiography. Planar and single-photon emission computed tomog-

raphy and computed tomography (SPECT/CT) acquisitions were performed. Selective internal radiotherapy was performed 8 to 15 days later at a second angiography, using glass microspheres. Activity administered was calculated with the aim of administering a dose of 120 Gy (within 20-Gy range) to the targeted liver volume (injected hemiliver) without exceeding a cumulative dose of 50 Gy to the lungs. Treatment personalization, with the aim to provide at least 205 Gy to the tumor using a treatment intensification (providing >150 Gy to the targeted liver) as previously described, was authorized.[22] Segmentation (targeted liver and tumor) was performed on SPECT/CT data as previously described.[23] Follow-up consisted of clinical evaluation, radiologic evaluation (CT scan), and blood testing (including hematologic, liver and renal function tests, carcinoembryonic antigen, carbohydrate antigen 19.9, and α-fetoprotein) between weeks 12 and 15, then every 8 weeks thereafter. In case of a secondary surgical procedure, follow-up was planned every 12 weeks. Follow-up was planned for 2 years after inclusion.

Outcomes

The primary end point was response rate (RR) according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 at 3 months, according to the review by investigators. Secondary objectives were toxic effects, PFS, OS, disease control rate (corresponding to patients with either stable disease or objective response at 3 months), quality of life, and RR according to Choi criteria.[24] Choi evaluation of response is based on evaluation of both sum of maximal diameter and density as measured in Hounsfield units. A decrease in density of at least 15% was accepted as a criterion of partial response according to Choi only if the absolute density change would account for at least 10 Hounsfield units. A planned central review analysis of response evaluation according to RECIST and Choi criteria was also performed by a single radiologist (L.B.). Toxic effects were assessed according to the National Cancer Institute-Common Terminology Criteria for Adverse Events, version 4.03.[25]

Statistical Analysis

The unacceptable RR threshold was defined as 22% (P0), and the expected RR threshold was defined as 45% (P1). Based on the Simon optimal 2-step design, with type I errors set at 5% and type II errors set at 10%, at least 41 patients were required to be included in the study. The Simon plan allowed us to stop the study prematurely for futility (after inclusion of 17 patients) if fewer than 5 patients were considered to be responders. In addition, it was expected during trial design that up to 5 patients could not be treated because of the contraindication shown on the planning angiogram. The final analysis would include the 41 treated patients (excluding patients not treated because of contraindication).

Data were summarized by median, minimum and maximum, and frequency for continuous data and percentage for categorical data. In particular, with respect to the primary end point, response rates are presented with 90% CIs, calculated using the exact Clopper-Pearson method.

Overall survival, PFS, and relapse-free survival curves were estimated using the Kaplan-Meier method. Overall survival was defined as the time between inclusion and death and PFS as the time between inclusion and progression or death. In patients with secondary surgical procedures, relapse-free survival was defined as the time between the surgical intervention and recurrence or death, and postsurgical OS was also presented as the time between surgical intervention and death. The factors associated with OS were also evaluated using a Cox proportional hazards regression model. A stepwise algorithm in forward direction using Bayesian information criteria was implemented to choose the final model. All the factors associated with OS at $P = .10$ were introduced in the multivariable analysis. The model assumptions were evaluated with Martingale and Schoenfeld residuals. Median follow-up was estimated using the reverse Kaplan-Meier method. Tolerance and safety were reported as a frequency table of Medical Dictionary for Regulatory Activities, version 18.1 preferred terms that occurred from the first arteriography to the end of follow-up and were or were not related to the experimental procedure. A post hoc analysis of liver toxic effects between patients with cirrhosis and patients without cirrhosis was performed because this measure was likely to explain some of the toxic effects observed. Statistical analysis was performed from March 31, 2017, to June 17, 2019.

Results

Population

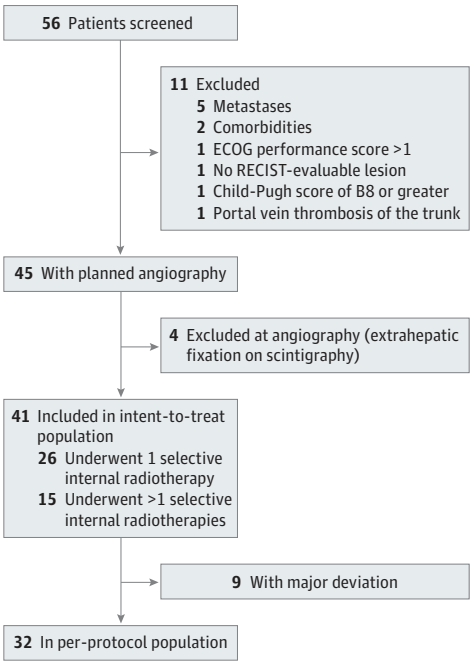
Between November 12, 2013, and June 21, 2016, 56 patients were screened; 45 fulfilled inclusion and noninclusion criteria before planning angiography, and 41 were included in the analysis of the intent-to-treat population without contraindication during angiography (4 excluded patients had extrahepatic fixation on scintigraphy) (**Figure 1**). Of 41 patients included in the study, 26 (63%) were male, with a mean (SD) age of 37 (36-82) years. The characteristics of the population are reported in **Table 1**.

Treatment Received and Safety

The median number of cycles of chemotherapy delivered was 6 (range, 1-15 cycles), with a relative dose intensity of 81% for gemcitabine and a relative dose intensity of 88% for cisplatin. Twenty-six patients (65%) had 1 SIRT session, 12 (30%) had 2 sessions, and 2 (5%) had 3 sessions (because of hepatic arterial anatomic features). The median dose delivered to targeted liver was 120 Gy (range, 18-430 Gy), the median dose delivered to the tumor was 317 Gy (range, 64-1673 Gy), and the median dose delivered to the nontumor liver was 87 Gy (range, 4-235 Gy). The numbers of patients in the intent-to-treat population with treatment-associated adverse events are reported in **Table 2**. Twenty-nine patients (71%) experienced grade 3 or 4 toxic effects.

More liver toxic effects occurred in the 12 patients with cirrhosis than in the patients without cirrhosis. Among patients with cirrhosis treated with SIRT without chemotherapy, 9 of 12 patients (75%) experienced hepatic failure (all grade asci-

Figure 1. Flowchart



ECOG indicates Easter Cooperative Oncology Group; RECIST, Response Evaluation Criteria in Solid Tumors.

Table 1. Patient Characteristics

Characteristic	Population[a]	
	Intent to Treat (n = 41)	Downstaged (n = 9)
Age at inclusion	67.3 (36.7-82.2)	71.2 (46.5-74.9)
Male sex, No. (%)	26 (63)	4 (44)
Cirrhosis, No. (%)	12 (29)	2 (22)
Child-Pugh score at inclusion among patients with cirrhosis, No. (%)	(n = 12)	(n = 2)
A5	9 (75)	2 (100)
A6	2 (17)	0
B7	1 (8)	0
ECOG performance status of 0 at inclusion (n = 40), No. (%)	26 (65)	7 (78)
Albumin, g/L (n = 39)	40 (24-47)	41 (39-44)
Prothrombin time, % vs control	89 (32-117)	90 (73-117)
Total bilirubin level at inclusion, μmol/L	13.3 (4-38)	13.6 (4-20.1)
ALT level, U/L	28 (10-346)	20 (10-346)
AST level, U/L	36 (12-138)	27 (12-115)
Alkaline phosphatase level, U/L	111 (49-366)	106 (52-300)
γ-Glutamyltransferase level, U/L (n = 40)	136.5 (25-613)	166 (61-597)
Carbohydrate antigen 19.9 level, IU (n = 40)	52 (0.6-32099)	36.5 (1-499)
Carcinoembryonic antigen level, ng/mL (n = 40)	3.1 (0.4-51)	2.4 (1-5.1)
Previous resection, No. (%)	5 (12)	0 (0)
Time from diagnosis to inclusion, d	48 (13-728)	63 (14-77)
Unifocal tumor, No. (%)	14 (34)	7 (78)
Tumor confined to 1 hemiliver, No. (%)	27 (66)	8 (89)
Liver hilar lymph nodes ≤3 cm, No. (%)	12 (29)	2 (22)
Abdominal lymph nodes, No. (%)	14 (34)	2 (22)
Lung metastasis ≤1 cm, No. (%)	7 (17)	0 (0)
Patient with locally advanced disease only, including hilar nodules, without abdominal lymph nodes or lung metastasis, No. (%)	24 (58)	7 (78)

Abbreviations: ALT, alanine transferase; AST, aspartate transferase; ECOG, Eastern Cooperative Oncology Group.

SI conversion: To convert ALT, alkaline phosphatase, AST, and γ-glutamyltransferase levels to microkatals per liter, multiply by 0.0167; albumin level to grams per deciliter, divide by 10; bilirubin level to milligrams per deciliter, divide by 17.104.

[a] Data are presented as median (interquartile range) unless otherwise indicated.

tes or jaundice with 5 nonreversible cases) vs 5 of 29 patients (17%) without cirrhosis (all reversible cases) (P = .001). In all cases of nonreversible toxic effects, patients had received whole-liver SIRT.

Outcomes

After a median follow-up of 36 months (95% CI, 26-51 months; range, 1-56 months), 40 patients were evaluable for response (1 patient died of causes related to disease progression and thus was evaluated as having progressive disease), 16 patients experienced disease progression, and 23 patients died. The primary end point, objective response assessed by investigator according to RECIST at 3 months was 39% (90% CI, 26%-53%). The disease control rate at 3 months was 98% (95% CI, 89%-99%) (40 of 41 cases). Results were confirmed by central review, with a best response rate of 41% (95% CI, 28%-55%) (17 of 41 cases) according to RECIST, and a Choi response rate of 93% (95% CI, 82%-98%) (38 of 41 cases). Results of central review of evolution of sum of maximal diameters and mean of density are shown on **Figure 2**.

Median PFS was 14 months (95% CI, 8-17 months), with a 12-month PFS rate of 55% (95% CI, 40%-71%) and 24-month PFS rate of 30% (95% CI, 16%-44%) (**Figure 3**A). Median OS was 22 months (95% CI, 14-52 months), with a 12-month OS rate of 75% (95% CI, 62%-89%) and 24-month OS rate of 45% (95% CI, 30%-61%) (Figure 3B).

Downstaging to Surgery

After treatment, 9 patients (22%) could be downstaged to surgical intervention. The initial reasons for nonresectability for these patients are reported in eTable 1 in the Supplement. Eight patients (20%) underwent R0 (microscopic-free margins) surgical resection. Among 27 patients with tumor involving only 1 hemiliver, surgery could be performed in 8 (30%). After a median postsurgical follow-up of 46 months, 2 recurrences and 3 deaths (2 due to disease progression and 1 due to postoperative liver dysfunction) were observed. Postsurgical OS curves are presented in Figure 3C, and relapse-free survival curves are presented in Figure 3D. For progression-free survival, the 12-month rate was 66.7% (95% CI, 35.9%-97.5%) and the 24-month rate was 66.77% (95% CI, 35.9%-97.5%); for postsurgical OS, the 12-month rate was 88.9% and the 24-month rate

was 88.9% (95% CI, 68.4%-100%). Examples of patients downstaged to surgical intervention are shown in the eFigure in the Supplement. Two patients with still unresectable cancer after treatment but with disease control were offered liver transplant. Cancer in both patients recurred at 16 and 17 months after liver transplant, and both cancers recurred with a single lung lesion. The lesions were resected in 1 patient and planned to be treated with stereotactic radiotherapy in the other patient. These 2 patients remained alive at 19 and 18 months after treatment.

Prognostic Model

We performed a Cox regression univariable and multivariable analysis of measures potentially associated with OS (eTable 2 in the Supplement). The measures that were independently associated with worse OS were decreased albumin level and elevated carcinoembryonic antigen level.

Discussion

The MISPHEC trial is, to our knowledge, the first published prospective trial regarding the effectiveness of SIRT in unresectable ICC. To our knowledge, this was the first prospective trial to evaluate the combination of chemotherapy and SIRT and the first multicenter report. The results showed activity of the strategy, with a response rate by RECIST of 39% and a high disease control rate at 3 months of 98%.[3] In addition, the median OS was 22 months, and the PFS was 14 months. A high proportion of patients were downstaged to surgical intervention and had favorable postsurgical outcomes. In addition, this strategy had an acceptable safety profile in patients without cirrhosis.

Previous retrospective data[6-19] on SIRT in patients with ICC were heterogeneous in terms of the population of patients included (chemotherapy-naive or previously treated patients with or without extrahepatic disease) and treatment type delivered (glass or resin microspheres; whether or not chemotherapy was used). Consequently, results are difficult to interpret, with a heterogeneous median OS ranging from 9 to 22 months. A systematic review and meta-analysis found a 28% response rate and a median OS of 15.5 months, with results suggesting the activity of the treatment, but advocated for prospective trials.[26] Another systematic review suggested that first-line treatment and combination with chemotherapy might be the best design for such a trial.[27] Another prospective trial of 25 patients with unresectable ICC that used glass microspheres in first-line treatment showed a response rate of 56%, a median PFS of 6 months, and a median OS of 22 months.[28] Some guidelines already proposed SIRT for locally advanced ICC in first-line[29] or second-line treatment.[30] The availability of prospective data will strengthen these recommendations, albeit randomized clinical trials are needed to demonstrate an improvement in OS. The SIRT Followed by CIS-GEM Chemotherapy Vs CIS-GEM Chemotherapy Alone as First Line Treatment of Patients With Unresectable Intrahepatic Cholangiocarcinoma (SIRCCA) phase 3 trial is currently randomizing patients with unresectable ICC to either chemotherapy alone or resin-microspheres SIRT followed by chemotherapy.

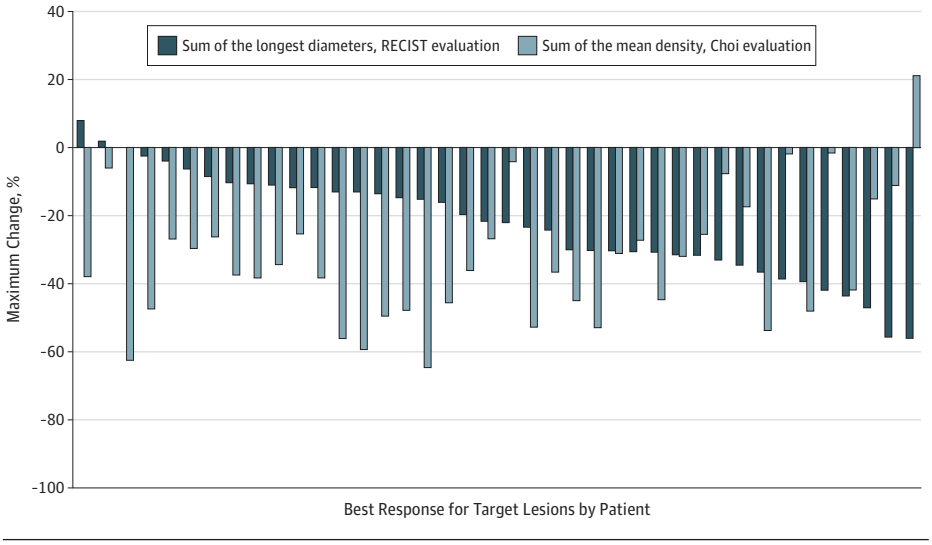
Table 2. Treatment-Related Adverse Events

System Organ Class, Preferred Term[a]	Patients With Adverse Event, No. (%)	
	Grade 1 or 2	Grade ≥3
Skin and subcutaneous tissue disorders		
Rash	9 (22)	0
Alopecia	5 (12)	0
Palmar-plantar erythrodysaesthesia syndrome	3 (7)	0
Ear and labyrinth disorders: hypoacousia or hyperacousia	2 (5)	0
Renal and urinary tract disorders: renal failure	3 (7)	0
Nervous system disorders		
Peripheral sensorimotor neuropathy	11 (27)	0
Taste alteration	8 (20)	0
Gastrointestinal tract disorders		
Nausea	18 (44)	2 (5)
Abdominal pain	12 (29)	5 (12)
Vomiting	12 (29)	1 (2)
Diarrhea	10 (24)	2 (5)
Dysphagia	2 (5)	0
Constipation	7 (17)	0
Ascites	2 (5)	3 (7)
Blood and lymphatic system disorders		
Neutropenia	9 (22)	21 (51)
Febrile neutropenia	0	1 (2)
Anemia	19 (46)	8 (20)
Thrombocytopenia	16 (39)	10 (24)
Lymphopenia	4 (10)	3 (7)
Hepatobiliary disorders		
Abnormal liver function test	5 (12)	1 (2)
Acute hepatic failure	1 (2)	2 (5)
Cholecystitis acute	1 (2)	1 (2)
Cholangitis	0 (0)	1 (2)
Respiratory, thoracic, and mediastinal disorders: epistaxis	4 (10)	0
Vascular disorders: venous thrombosis	2 (5)	1 (2)
Infections and infestations: oral fungal infection	5 (12)	0
Metabolism and nutrition disorders		
Decreased appetite	21 (51)	3 (7)
Weight decreased	8 (20)	1 (2)
General disorders and administration site conditions		
Asthenia	32 (78)	9 (22)
Pain	7 (17)	0
Mucosal inflammation	5 (12)	0
Edema	6 (15)	0
Administration site reaction	6 (15)	0
General physical health deterioration	0	2 (5)

[a] According to Medical Dictionary for Regulatory Activities, version 18.1.

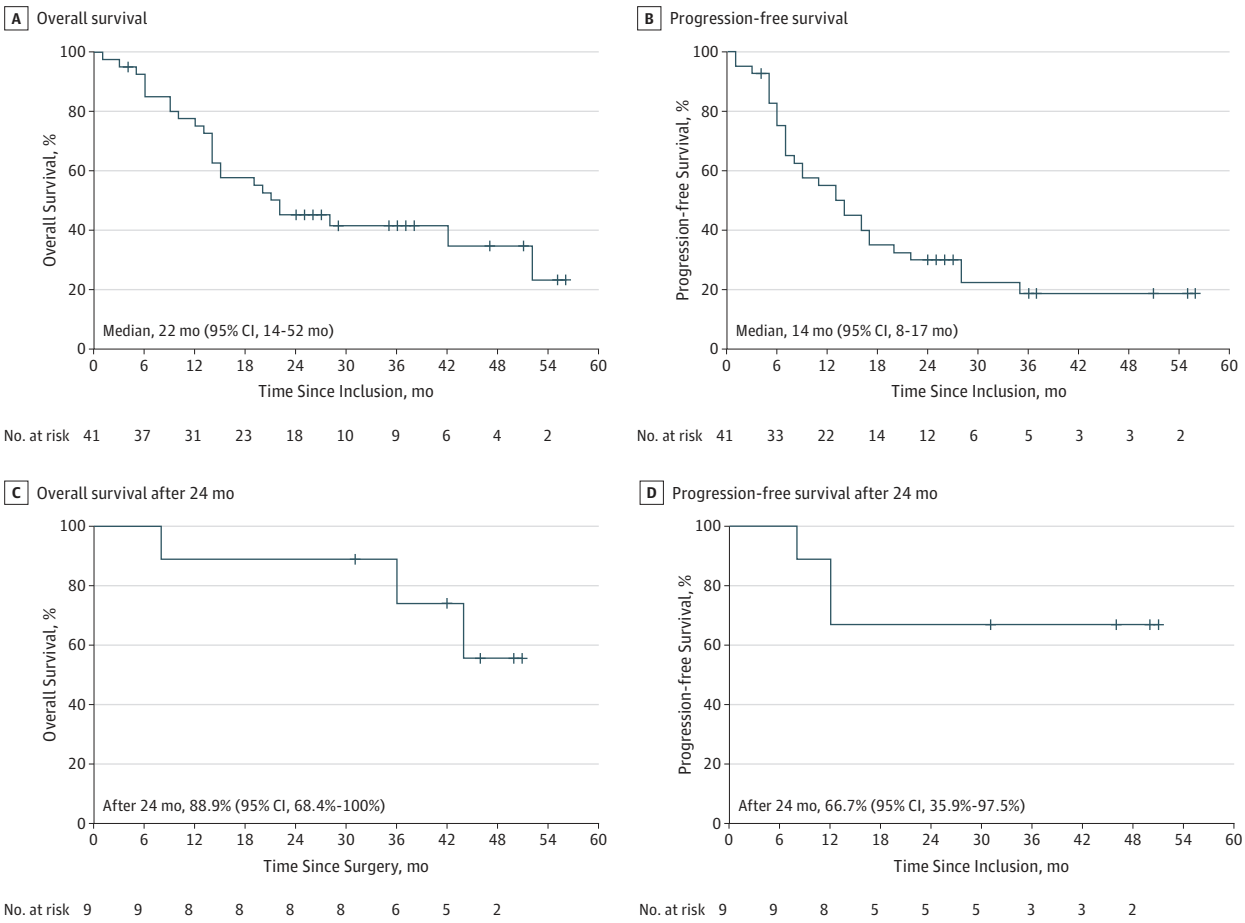
We showed in this trial that a high proportion of patients (30% of patients with disease involving only 1 hemiliver) could be downstaged to surgical intervention. Retrospective data not focusing on ICC suggest that surgical intervention is safe

Figure 2. Best Response for Target Lesions by Patient by Central Review



RECIST indicates Response Evaluation Criteria in Solid Tumors.

Figure 3. Progression-Free, Overall, and Relapse-Free Survival



A and B, Overall (A) and progression-free (B) survival in all patients in the intent-to-treat population. C and D, Overall (C) and relapse-free (D) survival among the 9 patients who underwent resection starting on the date of surgery.

after SIRT in selected patients.[31] We previously published data on patients with ICC who underwent resection after SIRT for ICC.[32] A retrospective analysis of patients receiving chemotherapy suggested that patients who could undergo resection after neoadjuvant chemotherapy and patients with upfront surgical intervention had similar outcomes.[33]

Furthermore, in this trial, the median follow-up was 46 months for the 9 patients who underwent resection, and the cumulative relapse-free survival rate was 67% at this time. These outcomes after surgical intervention were achieved in a population initially with unresectable tumors and are similar to those of recent adjuvant trials of patients with more heterogeneous initially resectable biliary tract cancer: the Gemcitabine and Oxaliplatin Chemotherapy or Surveillance in Resected Biliary Tract Cancer (PRODIGE 12) trial,[34] and the Capecitabine Compared With Observation in Resected Biliary Tract Cancer (BILCAP) trial.[35] This finding suggests that downstaging with SIRT combined with secondary surgical intervention has a potential for curative treatment in patients otherwise considered for palliative treatment.[36]

Other modalities of locoregional therapies were also studied among patients with ICC, including chemoembolization, intra-arterial chemotherapy, and external beam radiotherapy.[37,38] How these different modalities might compare with SIRT remain to be studied. A study is ongoing that compares SIRT with chemoembolization.[39]

Toxic effects shown in this trial were mainly consistent with chemotherapy-related toxic effects. Grade 3 or higher hematologic toxic effects were prevalent. It is possible that SIRT was associated with an increase in the frequency of this hematologic toxic effect; however, the chemotherapy dose-intensity was high and not limited by this toxic effect. By contrast, the number of hepatic toxic effects in patients with cirrhosis was high. Based on these results, we recommend that the concomitant use of chemotherapy and SIRT be avoided in patients with cirrhosis. In patients without cirrhosis, the liver toxic effect was acceptable and no irreversible liver toxic effect was seen.

Limitations

This study has some limitations. First, the single-arm nature of the study added difficulty to the interpretation of results. The outcomes in patients with locally advanced ICC might have been better than those in all patients with locally advanced or metastatic biliary tract cancers.[40] This study was performed in centers with experience with glass microspheres. The SIRT doses recommended in this study were defined using label instruction; however, accumulating evidence suggest that the definition of an appropriate dose delivered to the tumor, rather than a generic dose delivered to the targeted liver, might improve results.[41,42] Also, we did not have data on the molecular alterations present, which might influence outcomes.

Conclusions

Our study found activity of a combination of SIRT with chemotherapy as first-line treatment of ICC. The high disease control and downstaging rates suggest that this treatment can be an option in initially unresectable ICC. The postsurgical outcomes suggest that SIRT is a potentially curative strategy as downstaging treatment among patients otherwise considered for palliative-intent medical treatment. Furthermore, the safety profile was acceptable. These results should be confirmed by a phase 3 randomized clinical trial.

ARTICLE INFORMATION

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Author Affiliations: Department of Medical Oncology, Centre Eugène Marquis, Rennes, France (Edeline, Campillo-Gimenez, Pracht, Le Sourd, Boucher); Université Rennes, IndianaSERM, IndianaRA, Centre de Lutte contre le Cancer Eugène Marquis, Institut NUMECAN (Nutrition Metabolisms and Cancer), Rennes, France (Edeline); Centre Hospitalier Universitaire Nantes, Nantes, France (Touchefeu); Centre Hospitalier Universitaire Montpellier, Montpellier, France (Guiu); Centre Hospitalier Universitaire Beaujon, Clichy, France (Farge); Centre Hospitalier Universitaire Poitiers, Poitiers, France (Tougeron); Centre Hospitalier Universitaire Mondor, Créteil, France (Baumgaertner); Centre Hospitalier Universitaire Nancy, Nancy, France (Ayav); INSERM, LTSI U1099, Université Rennes 1, Rennes, France (Campillo-Gimenez); Radiology, Centre Hospitalier Universitaire Pontchaillou, Rennes, France (Beuzit); Gastroenterology, Centre Hospitalier Universitaire Pontchaillou, Rennes, France (Lièvre); Univ Rennes, Inserm, Regional Cancer Center Eugène Marquis, Chemistry Oncogenesis Stress Signaling-UMR1242, Rennes, France. (Lièvre); Hepatobiliary Surgery, Centre Hospitalier Universitaire Pontchaillou, Rennes, France (Boudjema); Radiology, Centre Eugène Marquis, Rennes, France (Rolland); Nuclear Medicine, Centre Eugène Marquis, Rennes, France (Garin).

Author Contributions: Drs Edeline and Campillo-Gimenez had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Edeline, Boucher, Garin.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Edeline, Touchefeu, Guiu, Beuzit, Boucher.
Critical revision of the manuscript for important intellectual content: Edeline, Touchefeu, Guiu, Farges, Tougeron, Baumgaertner, Ayav, Campillo-Gimenez, Pracht, Lièvre, Le Sourd, Boudjema, Rolland, Boucher, Garin.
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