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Real-World Efficacy of Radioembolization With or Without Chemotherapy in Patients with Locally Advanced Intrahepatic Cholangiocarcinoma

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Abstract

Background: Intrahepatic cholangiocarcinoma (iCCA) is the second most common primary liver malignancy and is associated with a poor prognosis. It is often diagnosed at an advanced stage, making it ineligible for curative treatments. The combination of locoregional therapies, such as selective internal radiation therapy (SIRT), and systemic therapies shows promise for locally advanced iCCA (LAiCCA). However, few studies have evaluated the benefit of SIRT in real-world practice.

Methods: This retrospective single-center study involved patients treated with SIRT for LAiCCA between 2016 and 2023.

Results: Of 28 patients treated with SIRT, 15 also received systemic therapy. The median overall survival was 17.1 months, with no significant difference between the groups (17.5 months for SIRT alone vs. 16.7 months for SIRT plus systemic therapy; hazard ratio: 1.573; 95% confidence interval: 0.524–4.722; p = 0.41). At the first reassessment, the objective response rate was 60.7% (similar between the groups), and the disease control rate was 75% (86.7% in the combined group vs. 61.5% in the SIRT-only group; p = 0.12). Four patients underwent surgical resection after treatment. SIRT was well tolerated, with only one grade > 1 adverse event reported.

Conclusion: SIRT demonstrated promising outcomes for LAiCCA in a real-world setting, with comparable survival outcomes irrespective of the addition of systemic therapy. For frail older patients with comorbidities, SIRT monotherapy could represent a viable and valuable alternative.

Keywords: Intrahepatic cholangiocarcinoma; Radioembolization; Selective internal radiation therapy; Systemic therapy.

Introduction

Cholangiocarcinomas (CCAs) are malignant tumors originating from the bile ducts and are classified into three main types based on their location: intrahepatic CCA (iCCA), which arises within the liver; perihilar CCA, located near the liver hilum; and extrahepatic CCA, which occurs in the bile ducts outside the liver. In recent decades, the global incidence of CCA has risen, with iCCA now recognized as the second most common primary liver malignancy [1]. Despite advancements in medical care, CCAs remain diseases with poor prognoses, and survival rates have shown little improvement over the past 30 years. Most cases are diagnosed at advanced stages, when curative treatments such as surgery, ablation, or liver transplantation are not viable anymore [2, 3]. Even among patients with iCCA, fewer than 15% are eligible for surgical intervention—the most effective treatment for localized

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tumors—because of the advanced stage of their disease at diagnosis [4]. Unfortunately, even for patients who undergo surgery, long-term outcomes remain discouraging. More than 50% of individuals with early-stage iCCA experience disease recurrence, with a median time to recurrence of only 20 months after surgical resection [5]. In cases of locally advanced intrahepatic cholangiocarcinoma (LAiCCA), one therapeutic strategy involves downstaging the tumor to enable curative treatment. Since the publication of the 2022 French guidelines, the standard of care in France has been to consider a combination of locoregional treatment and systemic therapy [6]. Among the available locoregional treatments, transarterial radioembolization—also known as selective internal radiation therapy (SIRT)—has shown particular promise. SIRT involves injecting microspheres loaded with the radioactive isotope Yttrium-90 directly into the tumor via an arterial approach. This technique has become a valuable tool in the management of unresectable primary and metastatic hepatic tumors [3, 7, 8].

In France, SIRT is approved as a first-line palliative treatment, either alone or in combination with systemic chemotherapy, for patients with unresectable or recurrent iCCA following resection. This approval applies to patients with a preserved Eastern Cooperative Oncology Group (ECOG) performance status of 0–1, intact liver function (Child–Pugh class A), and no evidence of extrahepatic disease [6]. A 2021 meta-analysis reviewed the effects of various locoregional treatments for CCA and highlighted the efficacy of SIRT in improving overall survival (OS) and progression-free survival (PFS) [9]. More recently, Edeline et al [10]. Evaluated the combination of gemcitabine and cisplatin (CISGEM) chemotherapy in treatment-naive patients through a phase II clinical trial. Their findings were encouraging, showing a 39% response rate, a substantial proportion of patients downstaged to surgery (22%), a median PFS of 14 months, and a median OS of 22 months. Despite these promising trial results, real-world data on the effectiveness of SIRT remain limited, and the potential benefit of combining SIRT with chemotherapy for intrahepatic disease has not been thoroughly explored yet. The objective of our retrospective, monocentric study was to evaluate the real-world effectiveness of SIRT in the treatment of LAiCCA at a French expert center. Additionally, we investigated the impact of adding chemotherapy to SIRT in routine clinical practice.

Materials and Methods

Study design

We conducted a single-center observational retrospective study at the University Hospital of Bordeaux, including all consecutive patients with LAiCCA treated with SIRT between 2016 and 2023.

Patients included in the study were aged 18 years or older, had been diagnosed with LAiCCA without extrahepatic disease, and were scheduled to undergo SIRT at our institution. Locally advanced disease was defined as involving critical vascular structures and/or regional lymph nodes. The exclusion criteria were the presence of other tumors such as hepatocellular carcinoma, combined hepatocellular carcinoma and CCA, extrahepatic CCA, gallbladder cancer, pancreatic cancer, and ampullary cancer. Patients were also excluded if contraindications were identified during work-up angiography, such as pulmonary or digestive shunts.

The decision to proceed with SIRT was made following recommendations from a multidisciplinary team discussion. All patients underwent pre-procedure imaging with computed tomography (CT) or magnetic resonance imaging (MRI), as well as follow-up CT or MRI within 3 months after the procedure.

Data collection

We prospectively collected data on the patients and their tumors. Clinical information included patient demographics and baseline characteristics such as age, sex, height, weight, body mass index, the presence of cirrhosis and its underlying cause, and the results of biological tests (carcinoembryonic antigen [CEA] level, carbohydrate antigen 19-9 (CA 19-9) level, liver function, albumin level, and creatinine level). Additionally, we recorded the ECOG performance status and tumor characteristics, including stage, unifocal or multifocal presentation, and the presence of vascular invasion. Details of the SIRT procedures were also documented, including pulmonary shunt assessment, the dosimetry administered to both the tumor and the non-tumoral liver tissue, and treatment-related outcomes, evaluated using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0.

Outcomes

The primary outcome was OS, defined as the time from the effective phase of SIRT to the date of death, last follow-up, or censoring. The secondary outcomes were PFS, defined as the time from SIRT to disease progression or detection of new lesions based on imaging (CT or MRI, evaluated using RECIST 1.1 criteria); the rate of subsequent surgical resection, measured as the number of patients who underwent surgery; and response metrics, including the response rate, disease control rate (DCR), and objective response rate (ORR). These metrics were assessed on the first post-SIRT imaging (CT or MRI) using RECIST 1.1 criteria and categorized as progression, stability, partial response, or complete response. DCR was defined as the sum of the complete response, partial response, and stable disease rates, while ORR included the complete and partial response rates. We also recorded the safety of the procedure, with adverse

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events evaluated according to NCI-CTCAE version 5.0, and identified factors associated with OS.

Statistical analysis

Continuous data are expressed as the median and interquartile range (IQR), while categorical variables are presented as percentages. All analyses used two-sided statistical tests, with a p-value of < 0.05 considered statistically significant. Survival data were analyzed using the Kaplan–Meier method, with comparisons assessed through the log-rank test. Univariate analysis was conducted using the Cox proportional hazards model, and variables with a p-value of < 0.20 were included in the multivariate model. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

Human ethics and consent to participate

The study was conducted in accordance with international guidelines, including Good Clinical Practice and the Declaration of Helsinki. In compliance with French national laws, the study received approval from a national Ethics Committee (CER-BDX 2024-187), and the Competent Authority (Agence Nationale de Sécurité du Médicament et des Produits de Santé) was notified. Data processing and usage adhered to the General Data Protection Regulation (EU 2016/679) and complied with the reference methodology outlined in French data protection laws.

Results

Patients' characteristics

In total, 38 patients with LAiCCA eligible for SIRT were initially screened for inclusion in the study (Supplementary Figure 1). Three patients were excluded at this stage: one was diagnosed with hepatocellular carcinoma, another had SIRT cancelled because of unfavorable histological findings, and the third was excluded because their SIRT procedure occurred after the inclusion cut-off date. Of the remaining 35 patients, all underwent the planned angiography. However, seven were excluded following this assessment. One patient declined to proceed with SIRT, while three others showed significant tumor progression on imaging performed the day before angiography. Additionally, one patient was hospitalized for cholangitis, and two were deemed ineligible for SIRT—one because of a high pulmonary shunt and the other because of difficulty accessing the hepatic artery. Ultimately, 28 patients received SIRT and were included in the analysis. Among these, 15 were treated with a combination of SIRT and systemic therapy. The baseline characteristics of the patients are summarized in Table 1. No significant differences were observed between those treated with SIRT combined with systemic therapy and those treated with SIRT alone. The median age at diagnosis was 69.5 years (IQR: 63.0–78.0 years), with an equal distribution of men and women. Cirrhosis was present in four (14.3%) patients, attributed to alcohol in two and to metabolic-associated steatotic liver disease in the other two. Liver function tests, including transaminase and bilirubin levels, were within normal limits for all patients. The median CEA level was 2.4 ng/mL (IQR: 1.4–4.0 ng/mL), while the CA 19-9 levels showed significant variability, with a median of 23.5 U/mL (IQR: 12.3–218.0 U/mL). All patients were in good general health, with ECOG performance scores of either 0 (50%) or 1 (50%). At diagnosis, Tumor, Node, Metastasis (TNM) staging revealed that six (21.4%) patients were classified as T1N0M0, seven (25.0%) as T2N0M0, seven (25.0%) as T3N0M0, two (7.1%) as T4N0M0, and six (21.4%) as N1.

The spheres used for SIRT were predominantly glass-microspheres (20 patients, 71.4%; TheraSphere®, Boston Scientific) (Table 2). The median administered dose was 2.01 GBq (IQR: 1.48–2.72 GBq). Regarding dosimetry, the median dose delivered to the tumor was 484.0 Gy (IQR: 360.5–620.0 Gy), while the median dose to the healthy liver was 45.8 Gy (IQR: 34.0–54.8 Gy). No significant differences were observed between the two groups (SIRT combined with systemic therapy vs. SIRT alone). For patients who received systemic therapy, 12 (80%) were treated with CISGEM, 1 (6.7%) with CISGEM and durvalumab, 1 (6.7%) with gemcitabine alone, and 1 (6.7%) with oral 5-FU (capecitabine) (Supplementary Table 1). Overall, treatment was well tolerated, with only one patient experiencing a grade > 1 adverse event (grade 2 hand–foot syndrome). Chemotherapy dose reductions were required in two patients: by 20% for the patient treated with capecitabine and by 50% for a patient on CISGEM. The mean number of treatment cycles was 5.53 and 11 (73.33%) patients had started systemic therapy prior to SIRT, with a mean interval of 4.18 months between the first cycle and the SIRT procedure.

Follow-up

At the first re-evaluation imaging (mean delay of 2.4 months), four patients achieved a complete response (14.3%) and 13 patients showed a partial response (46.4%). Disease stability was observed in four (14.3%) patients, while seven (25.0%) experienced tumor progression. The ORR was 60.7%, with 60.0% in the combined group and 61.5% in the SIRT-only group ($p = 0.46$). The DCR was 75.0%, with 86.7% in the combined group and 61.5% in the SIRT-only group ($p = 0.12$). During follow-up (Table 3), tumor progression was observed in 19 (67.8%) patients, including 10 (76.9%) in the SIRT-only group and 9 (60.0%) in the combined treatment group. Additionally, 16 (57.0%) patients received specific subsequent treatments, including 9 (69.0%) in the SIRT-only group and 7 (46.0%) in the combined treatment group. Fourteen patients (50%) died, evenly distributed between the combined treatment group (seven patients) and the SIRT-only group (seven patients). Additionally, two patients from

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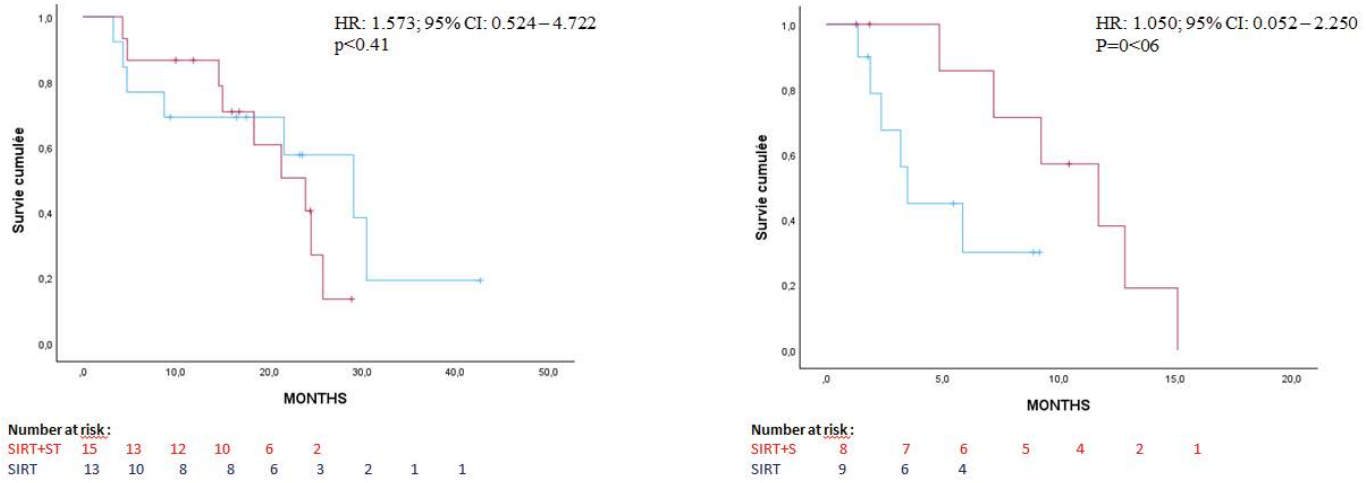

Figure 1: Outcomes in patients with CCA based on the treatment received: (A) OS, (B) PFS. Patients treated with SIRT + Yttrium-90 is represented in blue, and those treated with SIRT + systemic therapies are represented in red. Survival curves were generated using the Kaplan–Meier method and compared using the log-rank test. Statistical significance was defined as $p < 0.05$.

CCA: cholangiocarcinoma; OS: overall survival; PFS: progression-free survival; SIRT: selective internal radiation therapy; ST: systemic treatment

Table 1: Characteristics of patients with locally advanced intrahepatic cholangiocarcinoma who received SIRT with or without systemic therapy

	n	SIRT and systemic therapy	n	SIRT only	p-value
Women	8	53.3%	6	46.2%	0.7
BMI, median (IQR)	15	27.0 (21.0–30.0)	13	26.7 (24.2–28.1)	0.68
Age, median (IQR)	15	67.0 (62.0–73.0)	13	75.0 (67.0–79.0)	0.06
Presence of cirrhosis	2	13.3%	2	15.4%	1
Biological tests, median (IQR)					
AST	15	37.0 (28.0–42.0)	13	38.0 (36.0–45.0)	0.35
ALT	15	33.0 (24.0–78.0)	13	22.0 (18.0–28.0)	0.07
GGT	15	128.0 (49.0–261.0)	12	128.0 (65.0–475.5)	0.51
ALP	15	120.0 (91.0–158.0)	13	116.0 (93.0–227.0)	0.61
Bilirubin	15	7.5 (4.0–10.0)	13	11.0 (6.0–16.0)	0.13
Albumin	14	37.7 (34.3–42.0)	12	38.4 (34.4–42.1)	0.83
Creatinine	15	70.2 (57.0–82.0)	13	69.0 (56.0–78.0)	0.71
Tumor markers, median (IQR)					
CEA	14	1.7 (1.2–3.0)	11	2.6 (2.1–5.7)	0.2
CA 19-9	14	36.1 (10.9–269.0)	11	17.3 (12.3–218.0)	0.47
ECOG performance status	15		13		0.7
0	8	53.3%	6	46.2%	
1	7	46.7%	7	53.8%	
TNM staging	15		13		0.54
T1N0M0	2	13.3%	4	30.7%	
T2N0M0	3	20.0%	4	30.7%	
T3N0M0	4	26.7%	3	23.1%	
T4N0M0	2	13.3%	0	0.0%	
T2N1M0	2	13.3%	0	0.0%	
T3N1M0	2	13.3%	1	7.7%	
T4N1M0	0	0.0%	1	7.7%	

ALP: alkaline phosphatase; ALT: alanine transaminase; AST: alanine aminotransferase; BMI: body mass index; CA 19-9: carbohydrate antigen 19-9; CEA: carcinoembryonic antigen; ECOG: Eastern Cooperative Oncology Group; GGT: gamma-glutamyl transferase; IQR: interquartile range; SIRT: selective internal radiation therapy; TNM: Tumor, Node, Metastasis.

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Table 2: Characteristics of SIRT

	Global population (N = 28)	% or mean (IQR)	n	SIRT and systemic therapy	n	SIRT only	p-value
Type of spheres, n (%)	28		15		13		0.22
Resin-microspheres (SIR-Sphere®, Sirtex)	8	28.6%	6	40.0%	2	15.4%	
Glass-microspheres (TheraSphere®, Boston Scientific)	20	71.4%	9	60.0%	11	84.6%	
Pulmonary shunt, % Median (IQR)	27	2.10 (1.30–4.5)	14	1.75 (1–5.2)	13	2.95 (2.00–4.4)	0.34
Total injected dose, MBq Median (IQR)	26	2.01 (1.48–2.72)	14	1.81 (1.13–2.4)	12	2.50 (1.82–3.66)	0.1
Dose to the tumor, Gy Median (IQR)	20	484 (360.5–620)	9	439.3 (144.7–500)	11	550 (400–700)	0.19
Dose to healthy liver, Gy Median (IQR)	18	45.8 (34.0–54.8)	8	45.1 (21–52.4)	10	48.4 (40.0–68.9)	0.59

IQR: interquartile range; SIRT: selective internal radiation therapy

Table 3: Follow-up

	Global population (N = 28)	%	SIRT + chemotherapy group	%	SIRT only	%	p-value
Response at first imaging	28		15		13		0.08
Complete response	4	14.3%	1	6.7%	3	23.1%	
Partial response	13	46.4%	8	53.3%	5	38.4%	
Stability	4	14.3%	26.7	26.7%	0	0.0%	
Progression	7	25.0%	13.3	13.3%	5	38.4%	
Progression during follow-up	19	67.8%	9	60.0%	10	76.9%	0.43
Subsequent surgery	5	17.8%	4	26.7%	1	7.7%	0.33
Death	14	50.0%	7	50.0%	7	50.0%	0.7

IQR: interquartile range; SIRT: selective internal radiation therapy

the combined treatment group were lost to follow-up. Five patients (17.8%) underwent tumor resection surgery following initial treatment, including four (26.7%) from the combined treatment group and one (7.7%) from the SIRT-only group. Histological analysis of the resected tumors showed the presence of viable tumor cells in all specimens, although a significant portion of the tumors consisted of necrotic cells. Three of the patients received adjuvant chemotherapy. Of the remaining two, one died of surgical complications, and for the other, the multidisciplinary team determined that the "neoadjuvant" treatment was sufficient.

At the end of the follow-up, five (17.8%) patients were alive without any tumor progression, including three from the SIRT combined with systemic treatment group and two from the SIRT-only group.

Outcomes

The OS was 17.1 months (IQR: 9.6–24.1 months). For patients treated with SIRT and systemic therapy, the median survival was 16.7 months (IQR: 11.8–24.4 months), while for those treated with SIRT alone, it was 17.5 months (IQR: 8.7–23.5 months). There was no significant difference in OS between the two groups (hazard ratio [HR]: 1.573; 95% confidence interval [CI]: 0.524–4.722; p = 0.41) (Figure 1A). PFS was 5.4 months (IQR: 1.9–9.2 months) for the entire population. Patients treated with SIRT and systemic therapy had a median PFS of 9.2 months (IQR: 3.3–12.2 months), compared with 3.3 months (IQR: 1.8–6.6 months) for those treated with SIRT alone. However, the difference between the two groups was not statistically significant (HR: 1.050; 95% CI: 0.052–2.250; p = 0.06) (Figure 1B). The rate of subsequent tumor resection was 17.0% for the entire population, with 26.7% in the combined treatment group and 7.7% in the SIRT-only group. There was no significant difference between the two groups.

Prognosis

In the univariate analysis of factors associated with OS (Table 4), age above the median of 69.5 years (p = 0.03; HR: 4.282; 95% CI: 1.113–16.465) and high creatinine level above the median of 69.6 µmol/L (p = 0.02; HR: 4.509; 95% CI: 1.277–15.925) were significantly associated with poorer

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Table 4: Factors associated with OS in the cohort examined in this study

Factors associated with overall survival	Unadjusted HR (95% CI)	Wald p	Multivariable-adjusted HR (95% CI)	Wald p
Sex	0.345 (0.109–1.094)	0.07		
BMI	0.977 (0.908–1.051)	0.52		
Age (> 69.5 vs. ≤ 69.5 years)	4.282 (1.113–16.465)	**0.03**	1.097 (1.014–1.188)	0.02
AST	0.989 (0.961–1.018)	0.47		
ALT	0.99 (0.971–1.010)	0.33		
GGT (> 128.0 vs. ≤ 128.0)	1.776 (0.638–4.945)	0.27	1.005 (1.001–1.009)	0.01
ALP	1.002 (0.997–1.006)	0.43		
Bilirubin	0.981 (0.913–1.055)	0.61		
Albumin	0.994 (0.892–1.107)	0.91		
Creatinine (> 69.6 vs. ≤ 69.6)	4.509 (1.277–15.925)	**0.02**	8.137 (1.161–57.037)	0.03
CEA (> 2.4 vs. ≤ 2.4)	2.916 (0.926–9.188)	0.06	4.775 (1.157–19.711)	0.03
CA 19-9	1.000 (1.000–1.000)	0.87		
ECOG	1.07 (0.395–2.894)	0.89		
TNM	0.958 (0.707–1.299)	0.78		
Response	1.148 (0.682–1.931)	0.6		
Dose reduction	3.723 (0.429–32.312)	0.23		

ALP: alkaline phosphatase; ALT: alanine transaminase; AST: alanine aminotransferase; BMI: body mass index; CA 19-9: carbohydrate antigen 19-9; CEA: carcinoembryonic antigen; CI: confidence interval; ECOG: Eastern Cooperative Oncology Group; GGT: gamma-glutamyl transferase; HR: hazard ratio; IQR: interquartile range; OS: overall survival; TNM: Tumor, Node, Metastasis.

OS. After multivariate Cox regression analysis, the factors significantly associated with OS were age (p = 0.02; HR: 1.097; 95% CI: 1.014–1.188), creatinine level > 69.6 µmol/L (p = 0.03; HR: 8.137; 95% CI: 1.161–57.037), high GGT level (p = 0.01; HR: 1.005; 95% CI: 1.001–1.009), and high CEA level above the median of 2.4 ng/mL (p = 0.03; HR: 4.775; 95% CI: 1.157–19.771).

Discussion

As the incidence of iCCA continues to rise, the treatment landscape faces considerable challenges, highlighting the need for effective strategies such as SIRT. Our study adds to the growing body of evidence by assessing the efficacy of SIRT in a real-world clinical setting, offering insights that complement previous findings from clinical trials. In our retrospective analysis of 28 patients with LAiCCA, we observed an OS of 17.1 months, with no significant difference between patients treated with SIRT alone and those receiving SIRT combined with systemic therapy. While these findings align with some of the promising outcomes reported in clinical trials, such as those by Edeline et al., [10] which highlighted improved PFS with combined treatments, our study underscores the real-world applicability of SIRT. Although OS and PFS in our study are not as favorable as those reported in the MISPHEC trial, our findings align with a 2021 meta-analysis that included 22 cohorts on SIRT and reported an OS of 14.1 months [9, 10]. This variability in outcomes underscores the need for further research, particularly randomized controlled trials, to better define the role of SIRT in the treatment of LAiCCA. The strength of our study lies in its focus on real-world patient experiences, demonstrating the efficacy of SIRT beyond the controlled environment of clinical trials. Conducted at an expert referral center with extensive experience in SIRT administration and side-effect management, the study benefited from a robust patient recruitment process, ensuring diverse representation. By adopting a single-institution approach, we ensured consistent treatment protocols and standardized patient monitoring, enabling a comprehensive evaluation of treatment outcomes and adverse events. Additionally, our analysis incorporated detailed patient demographics and treatment-related data, providing valuable insights into the impact of SIRT in routine clinical practice.

However, the retrospective design of our study presents inherent limitations. Additionally, the single-center nature and small sample size introduce biases that may affect

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the statistical power and generalizability of our findings. Despite these constraints, the two groups (SIRT only and SIRT with systemic therapy) were comparable in baseline characteristics, including tumor staging, liver function, and demographic factors. This similarity between the groups minimizes the influence of potential confounding factors, thereby strengthening the validity of our comparisons and enabling a more reliable assessment of the outcomes associated with each treatment strategy. Our findings align with growing evidence supporting SIRT as an effective treatment for unresectable iCCA, offering impressive disease control as demonstrated by the ORR, DCR, and ability to achieve downstaging in some cases, facilitating access to curative treatments. This is consistent with outcomes from the MISPHEC trial, particularly in our cohort's combination therapy group [10]. Notably, in our study, treatment led to tumor downstaging, as reflected by improved TNM classifications in four of the five patients who underwent surgery (three in the combined treatment group and one in the SIRT-only group) compared with their pretreatment staging. Tumor recurrence rates were similar between the two groups, suggesting a favorable therapeutic response that enhanced the potential for surgical intervention.

As a targeted therapy, SIRT delivers localized tumor treatment with limited systemic toxicity, making it a viable option for frail patients who may not tolerate more aggressive treatments such as chemotherapy or surgery due to comorbidities, poor performance status, or liver dysfunction. In our study, SIRT demonstrated promising disease control and provided palliative benefits for patients with advanced or inoperable CCA, including those considered frail. Studies have shown that SIRT can lead to tumor shrinkage, symptom improvement, and potentially extended survival in such patients. Additionally, SIRT offers the potential to reduce the tumor burden, alleviate biliary obstructions, and manage symptoms such as pain or jaundice. By directly addressing these issues, SIRT can improve patients' quality of life while minimizing the risks associated with more aggressive systemic therapies or surgical interventions. Recent advancements, such as the personalized dosimetry approach demonstrated in the LEGACY trial [11]. Underscore the potential for improved outcomes through innovative techniques. One such method, radiation segmentectomy, involves selective radioembolization of the tumor-bearing hepatic segment, enabling the delivery of higher radiation doses while sparing unaffected liver tissue. This technique has shown consistently strong response rates. In a subset analysis correlating radiation dose with pathology in resection or transplantation, LEGACY patients achieved complete pathological necrosis when the dose to the tumor-bearing tissue exceeded 400 Gy, establishing this threshold as critical for an ablative effect. This approach was implemented for all patients in our study, demonstrating its feasibility in real-world settings, with a mean tumor dose of 484 Gy, exceeding the established threshold. In the DOSISPHERE trial, [12] a prospective randomized study, the application of personalized multicompartment dosimetry more than doubled the median OS, from 10.7 to 26.6 months, compared with patients treated using standard dosimetry. However, it is important to note that both the LEGACY and DOSISPHERE trials exclusively included patients with hepatocellular carcinoma, which may account for the differences in survival outcomes compared with our study focused on patients with iCCA. In the future, enriching the evidence base with randomized trials will be crucial, including the ongoing phase III SIRCCA trial, which is evaluating the benefit of adding SIRT to CISGEM chemotherapy as a first-line treatment for patients with iCCA. These studies will provide valuable insights into optimal treatment protocols and help identify the patient populations most likely to benefit from SIRT. In our study, only one patient received a combination of SIRT, chemotherapy (CISGEM), and durvalumab, despite this combination being recommended for advanced iCCA following the positive results of the phase III TOPAZ-01 trial [13]. The limited use of immunotherapy in this real-world setting highlights an area for improvement in future treatment protocols. Incorporating immunotherapy could potentially enhance the efficacy of SIRT through the abscopal effect, a phenomenon where localized treatment induces systemic tumor control [14].

In conclusion, our findings support the role of SIRT as an important therapeutic option in the management of LAiCCA, while also underscoring the need for further research. As oncology continues to advance, understanding the true efficacy of treatments such as SIRT will be critical for optimizing patient care and improving outcomes in this challenging disease. This study provides a foundation for future investigations, particularly into the combination of SIRT with systemic therapies, including immunotherapy, which shows promise. While SIRT may not be curative, it serves as a valuable palliative option, improving quality of life and potentially extending survival, particularly in vulnerable and high-risk patients.

Abbreviations

CA 19-9:	carbohydrate antigen 19-9
CEA:	carcinoembryonic antigen
CI:	confidence interval
CISGEM:	cisplatin-gemcitabine regimen
CT:	computed tomography
DCR:	disease control rate
ECOG:	Eastern Cooperative Oncology Group
GBq:	GigaBecquerel
HR:	hazard ratio
iCCA:	intrahepatic cholangiocarcinoma

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IQR:	interquartile range
LAiCCA:	locally advanced intrahepatic cholangiocarcinoma
MRI:	magnetic resonance imaging
NCI-CTCAE:	National Cancer Institute Common Terminology Criteria for Adverse Events
ORR:	objective response rate
OS:	overall survival
PFS:	progression-free survival
RECIST:	Response Evaluation Criteria in Solid Tumors
SIRT:	selective internal radiation therapy
TNM:	Tumor, Node, Metastasis

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Jean-Frédéric Blanc declares conflicts of interest with Servier, Tahio Oncology, Incyte, MSD, Astrazeneca, Roche, and Boston Scientific.

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Authors' contribution

- Study concept and design: GA, JFB, MD
- Acquisition of data: GA, DP, SB
- Analysis and interpretation of data: GA, VA, MD
- Drafting of the manuscript: GA, JFB, MD
- Critical revision of the manuscript for important intellectual content: GA, JFB, MD
- Guarantor of the article: MD

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