Twenty Years of Radiation Therapy of Unresectable Intrahepatic Cholangiocarcinoma: Internal or External? A Systematic Review and Meta-Analysis

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Keywords

Cholangiocarcinoma · Radioembolization · Radiation therapy · Interventional radiology · Radiation oncology

Abstract

Purpose: Both external beam radiation therapy (EBRT) and selective-internal radiation therapy (SIRT) are implemented to treat unresectable intrahepatic cholangiocarcinoma (iCCA). The present study aimed to evaluate the efficacy of EBRT and SIRT in managing iCCA through a systematic review and meta-analysis. **Methods:** PubMed and Cochrane database were queried to search for studies published from January 2000 to June 2020 without language restrictions. Median survival time, overall survival, and radiological response were extracted. Secondary outcomes such as complication rates, predictors of survival, and downstage to surgery were pooled. Patient-level survival data were obtained to generate Kaplan-Meier survival graph. Pooled outcomes were analyzed with a random-effect model. **Results:** Twenty-nine and 20 studies including 732 and 443 patients from the SIRT and EBRT groups were included in the present study. From initial radiation treatment, the median survival time for patients who underwent SIRT and EBRT were 12.0 (95% confidence interval [CI]: 10.8–14.6) and 13.6 (95% CI: 11.1–16.0)

months, respectively. As first-line therapy, the median survival time was 36.1 (95% CI: 20.6–39.5) months for SIRT and 11.0 (95% CI: 9.3–13.6) months for EBRT. Both radiation modalities were effective in downstaging initially unresectable iCCA to surgery (SIRT: 30.5%; EBRT: 18.3%). Patients in the SIRT group encountered more post-embolization abdominal pain (6.9 vs. 2.2%), ulcer (1.0 vs. 0.5%), nausea (1.6 vs. 0.7%), anorexia (5.9 vs. 0%), thrombocytopenia (7.3 vs. 6.0%), hyperbilirubinemia (5.2 vs. 2.1%), and hypoalbuminemia (13.2 vs. 3.3%), whereas EBRT was associated with higher rates of anemia (0.6 vs. 7.5%) and neutropenia (6.5 vs. 11.0%). **Conclusions:** Both EBRT and SIRT were safe and effective in treating unresectable iCCA. However, available evidence was highly heterogeneous regarding patient population, limiting fair comparison between 2 radiation modalities. Future high-quality comparative studies are warranted.

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Introduction

Intrahepatic cholangiocarcinoma (iCCA) is a primary hepatic malignancy arising from peripheral intrahepatic bile ducts [1]. While rare, a notable increasing trend has been observed worldwide in terms of incidence and mor-

tality [2–4]. Clinically, iCCA typically follows an indolent progression with nonspecific symptoms, presenting as advanced disease upon initial diagnosis [5]. While surgical resection offers potentially curative treatment to iCCA, 63–85% is considered unresectable at the time of diagnosis [1, 6]. In addition, postoperative recurrence is frequent during follow-up, with a dismal 5-year survival of 20–35% [7–10]. For patients with locally advanced and unresectable iCCA, in addition to traditional systemic chemotherapy, liver directed therapy options including embolotherapy, radiotherapy, and direct hepatic arterial infusion all demonstrate promising data [11]. Efficacy and superiority of these treatments are however challenged by a lack of randomized-controlled trials.

Within the last decade, a growing amount of evidence has been published favoring the use of radiotherapeutic modalities for iCCA [12–15]. According to the International Liver Cancer Association and National Comprehensive Cancer Network guidelines, both selective-internal radiation therapy (SIRT) and external beam radiation therapy (EBRT) are acceptable approaches for locally advanced and unresectable iCCA [11, 16]. A recent study utilizing the National Cancer Database, suggested an increased overall survival (OS) benefit with stereotactic-body radiation therapy (SBRT) over conventional chemoradiation (CRT) and transarterial radioembolization [17]. However, this study had several methodological limitations including significantly different baseline characteristics, small sample size (87 patients in the propensity-weighted analysis), and lack of data on treatment-related toxicities. Current recommendations for EBRT versus SIRT are not bolstered by high-quality evidence. Therefore, the purpose of the present study was to characterize the safety and efficacy of EBRT and SIRT for the treatment of iCCA through a systematic review and meta-analysis.

Methods

Literature Screening

The study was performed in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis guideline. PubMed and Cochrane Library were queried from establishment to June 2020 without language restriction. The following terms were used:

1. “cholangiocarcinoma” AND (“radioembolization” OR “yttrium”) for radioembolization;
2. “cholangiocarcinoma” AND (“radiation” OR “radiotherapy”) for external radiation therapy.

The following inclusion criteria were adopted: (a) patient was diagnosed with iCCA and received EBRT or SIRT; (b) clinical fol-

low-up data including radiological response and/or survival rates were reported. A study was excluded if the following criteria were met: (a) nonhuman studies; (b) case report and study with sample size ≤ 5 patients; (c) absence of original data (letter, editorial, commentary, and review); (d) population-level study; (e) clinical outcomes were not selectively reported for patients with iCCA and received SIRT or EBRT; (f) studies published prior to the year of 2000; (g) studies solely focusing on adjuvant RT for post-resection iCCA; and (h) studies focusing on mixed-type HCC-CCA.

Endnote X8 (Clarivate Analytics, Philadelphia, PA) was used to identify and remove duplicates. Articles were initially screened based on titles, abstracts, and keywords, followed by a comprehensive review of full text of the remaining studies. Literature pertaining to RE and RT was queried and screened separately. A detailed screening process is depicted in online suppl. Figure 1 (for all online suppl. material, see www.karger.com/doi/10.1159/000516880).

Data Acquisition

The primary end points of interest were median survival time (MST), OS, and degree of radiographic response. Secondary end points were treatment-related adverse events, predictor analysis of OS (hazard ratio [HR]), and ability to downstage to surgery. In addition, the following baseline characteristics were retrieved: author, year, country, study design, treatment modality (EBRT vs. SIRT), sample size, age, sex, tumor number, tumor size, Eastern Cooperative Oncology Group Status (ECOG) performance, metastasis status, unilobar versus bilobar disease, tumor burden, infiltrative versus peripheral type, presence of cirrhosis, previous treatment history, radiation dosage, pulmonary lung fraction, the presence of portal venous invasion (PVI), and activity prescription method. Information regarding regions and institutions where studies were conducted was collected the last to minimize bias.

Measures of radiographic response, classified as complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD), were extracted along the imaging evaluation methods. Response rate (RR) was defined as the combined rates of CR and PR; disease control rate (DCR) was defined as the combined rates of CR, PR, and SD.

The MST and OS at 6 months, 1 year, 2 years, and 3 years were extracted. Individual patient survival outcomes were retrieved from survival curves of the original studies using GetGraph Digitizer v 2.26 (<http://getdata-graph-digitizer.com/>). Studies that did not label censored data (tick) were excluded from this analysis, as the survival outcomes of these patients could not be derived. Reasons of exclusion were tabulated (online suppl. Tables 1.1, 1.2). OS rate was pooled on Kaplan-Meier survival curve. MST and cumulative survival rates at 6 months, 1 year, 2 years, and 3 years were calculated.

The quality of each study was assessed with the methodological index for nonrandomized studies (online suppl. Table 2). Two authors retrieved the data independently. Any disagreement was resolved upon discussion.

Statistical Analysis

All quantitative analyses were performed with Stata 15.1 (STATA Corp., College Station, TX, USA). Meta-analysis was conducted with *-metan* and *-metaprop* one functions [18, 19]. Radiological response, HR of predictive analysis, and adverse events were pooled and reported in weighted means with 95% Wald confidence intervals (CIs). A random-effect model was adopted due to

the cross-study heterogeneity. Publication bias was analyzed with Egger's test and by assessing asymmetries on the funnel plot. For studies sharing overlapping patient sample, only the study with the largest sample size was included in the quantitative analysis for the variable of interest. Log-rank test was implemented to compare survival outcomes between groups. p value <0.05 was considered significant.

Results

Baseline Characteristics

Among the initial 150 unique search results, 29 original studies from 17 groups of investigators were screened and considered in the meta-analysis of the SIRT [14, 20–47] (online suppl. Fig. 1a). A total of 732 patients received SIRT (Table 1); the median/mean age ranged from 66.4 to 69.3 years old. The female versus male ratio, tumor number, distribution, size, and ECOG performance score of each study are specified in Table 1. The median/mean percentage of extrahepatic metastasis at diagnosis, presence of cirrhosis, presence of PVI, and lung shunt fraction were 12.3–57.9, 0–35, 0–81.1, and 4.4–7%, respectively. The mean/median delivered radiation activity and dosage ranged from 1.20 to 1.76 GBq and 92.7–322 Gy, respectively. Among 9 studies that reported tumor burden relative to liver parenchyma, the total percentage of patients with $<25\%$ tumor burden was 111/272 (40.8%). Most patients received another form of anticancer treatment prior to the SIRT (Table 1). Only 2 studies (2/17) focused solely on treatment-naïve patients (11.8%). Concomitant chemotherapy was administered in all enrolled patients in 5/12 studies (41.7%).

Regarding EBRT, 20 unique studies from 15 institutions were included in the present meta-analysis [13, 48–66] (online suppl. Fig. 1b). The following radiation modalities were used: 5 photon-based conventional dose radiotherapy (CRT), 5 photon-based SBRT, 2 proton therapy (PT), 1 carbon-ion radiotherapy, and 3 studies utilized both photon/proton EBRT (1 conventional dosed, 1 ablative, and 1 hypofractionated). A total of 443 patients received RT (Table 2); the mean/median age ranged from 57 to 76 years old. The female/male ratio, tumor number, size, ECOG performance, distribution, peripheral versus infiltrative type was listed in Table 2. Tumor burden was not reported. Only Tse et al. [63] reported the percentage of PVI at diagnosis (30%). The median/mean BED ranged from 50.1 to 109.3 Gy. Excluding studies that did not specify previous treatment history, only 7/16 (43.8%) studies involved patients who were treatment-naïve prior to RT (Table 2). Concomitant che-

motherapy was administered in all enrolled patients in 3/10 studies (70.0%).

Radiological Response

For SIRT, the pooled RR according to response evaluation criteria in solid tumors (RECIST), modified RECIST (mRECIST), European Association for the Study of the Liver (EASL), World Health Organization (WHO), and Positron Emission Tomography Response Criteria in Solid Tumors (PERCIST) were 22% (95% CI: 10–37%), 35% (95% CI: 4–75%), 82% (95% CI: 48–100%), 24% (95% CI: 14–39%), and 81% (95% CI: 63–95%), respectively (Fig. 1a). The pooled DCR were 75% (95% CI: 65–84%), 78% (95% CI: 64–89%), 98% (95% CI: 88–100%), 98% (95% CI: 88–100%), and 100% (95% CI: 93–100%) based on RECIST, mRECIST, EASL, WHO, and PERCIST, respectively (Fig. 1b). The funnel plot did not suggest significant difference among RR (Egger's test: $p = 0.276$) and DCR (Egger's test: $p = 0.559$) based on RECIST criteria (online suppl. Fig. 2a, b). Among the studies reporting RECIST criteria, $I^2 = 89.9\%$ ($p < 0.01$) and 76.7% ($p < 0.01$) for RR and DCR, respectively.

For EBRT, the pooled RR based on RECIST, mRECIST, and EASL were 31% (95% CI: 12–54%), 46% (95% CI: 30–64%), and 36% (95% CI: 22–51%), respectively (Fig. 1c). The DCR was 83% (95% CI: 61–98%), 89% (95% CI: 73–96%), 84% (95% CI: 71–94%) according to RECIST, mRECIST, and EASL, respectively (Fig. 1d). Based on RECIST criteria (online suppl. Fig. 2c, d), funnel plot did not suggest significant difference among RR (Egger's test: $p = 0.407$) and DCR (Egger's test: $p = 0.252$). The RR of SBRT (48%, 95% CI: 26–70%) was higher than CRT (31%, 95% CI: 19–43%); the DCR of PT (99%, 95% CI: 95–100%) was higher than SBRT (73%, 95% CI: 52–91%) and CRT (71%, 95% CI: 36–92%; online suppl. Fig. 3). Among the studies reporting RECIST criteria, $I^2 = 77.5\%$ ($p < 0.01$) and 83.9% ($p < 0.01$) for RR and DCR, respectively.

Survival

For patients who received SIRT, the MST of included studies ranged from 6.3 to 33.6 months (Table 3). OS at 6 months, 1 year, 2 years, and 3 years were 56–100, 32.6–97.3, 5–68.6, and 0–46.2%, respectively. In terms of per-patient analysis, survival data of 450 individual patients were successfully obtained from 12 studies (Fig. 2a). The MST was 12.0 (95% CI: 10.8–14.6) months from the time of first SIRT treatment. The cumulative OS rates at 6 months, 1 year, 2 years, and 3 years were 74.7% (70.3–78.5%), 52.3% (47.4–57.0%), 33.3% (28.7–37.9%), and 25.3% (21.1–29.6%), respectively.

Table 1. Baseline characteristics of patients that underwent radioembolization

Study	Sample size	Age	Sex (female:male)	Tumor number	Tumor size, cm	ECOG	Metastasis	Cirrhosis	Unilobar vs. bilobar	Infiltrative vs. peripheral	Portal vein invasion	Dose	Tumor burden	Lung shunt fraction	Prior treatment	Concomitant chemotherapy
Akinwande et al. [20]	25	64	17:8	NR	NR	0-2: 24 >2: 1	11/25 (44.0%)	NR	NR	NR	NR	1.56 GBq	<25%: 12 25-50%: 9	NR	Chemotherapy: 13/25 (52%) Resection/ablation: 5/25 (20%)	4/25 (16.0%)
Beuzit et al. [23]*	45	64	21:24	≤3: 26 >3: 19	6	0: 25 1-2: 20	NR	8/45 (18%)	NR	NR	NR	NR	NR	NR	Chemotherapy: 41/45 (91%) TACE: 1/45 (2.2%) RFA: 2/45 (4.4%)	13/45 (28.9%)
Edeline et al. [14]*	24	64	10:14	1: 15 >1: 9	7.9	0: 12 1: 9 2: 3	0	5/24 (21%)	NR	NR	5/24 (21%)	2.25 GBq 256 Gy	NR	1%	Naive: 24/24 (100%)	24/24 (100%)
Edeline et al. [24]*	41	64.0	15:26	1: 14 >1: 27	NR	0: 26 1: 15	17/41 (41.5%)	12/41 (29.3%)	NR	NR	0	317 Gy	NR	NR	Resection: 5/41 (12.2%)	41/41 (100%)
Manceau et al. [21]*	35	64.7	18:17	NR	7.9	0: 26 1: 9	0	9/35 (25.7%)	10 vs. 25	28 vs. 7	8/27 (22.9%)	2.6 GBq 322 Gy	NR	NR	NR	35/35 (100%)
Rayar et al. [47]*	8	68	5:3	8	9.2	0-4 1: 4	0	0	3 vs. 5	NR	1/8 (12.5%)	2 GBq	NR	NR	NR	8/8 (100%)
Riby et al. [46]*	19	66	10:9	1: 13 >1: 6	7	NR	0	0	NR	NR	NR	1.965 GBq 258 Gy	NR	NR	Naive: 19/19 (100%)	19/19 (100%)
Buettner et al. [1, 32]	115	NR	60:55	1: 30 >1: 85	7.2	0-44 1: 63 2: 6 3: 1	27/115 (24%)	9/115 (8%)	33 vs. 82	NR	2/115 (1.7%)	1.7 GBq	NR	4.8%	Resection: 17/115 (15%) Chemotherapy: 91/115 (79%)	NR
Camacho et al. [39]**	9	58	5:4	<5: 5 >5: 4	6.6	0: 5 1: 4	NR	NR	NR	NR	NR	NR	NR	NR	Resection: 4/9 (44.5%) Chemotherapy: 9/9 (100%)	0/9 (0%)
Rafi et al. [22]**	19	63.3	12:7	1: 6 >1: 13	≤5: 3 >5: 15	0: 1 1: 14 2: 4	11/19 (57.9%)	NR	11 vs. 8	NR	NR	1.195 GBq	NR	NR	Chemotherapy: 19/19 (100%) TACE: 4/19 (21%) Resection: 0	0/19 (0%)
Xing et al. [40]**	40	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	7.0%	NR	NR
Filippi et al. [25]***	17	59.4	11:6	1: 5 >1: 12	NR	NR	4/17 (23.5%)	NR	14 vs. 3	NR	NR	1.3 GBq	NR	NR	Chemotherapy: 11/17 (64.7%) Resection: 4/17 (23.5%) Naive: 2/17 (11.8%)	NR
Filippi et al. [27]***	9	65.4	4:5	NR	NR	NR	2/9 (22.2%)	NR	NR	NR	NR	1.4 GBq	<25%: 9	NR	Chemotherapy: 7/9 (77.8%) Resection: 2/9 (22.2%) RFA: 1/9 (11.1%)	NR
Filippi et al. [26]***	20	64.7	11:9	NR	NR	NR	8/20 (40%)	7/20 (35%)	NR	NR	NR	1.6 GBq	NR	NR	Chemotherapy: 10/20 (50%) Resection: 8/20 (40%) Ablation: 1/20 (5%) Radiation: 1/20 (5%) Naive: 2 (10%)	NR
Mosconi et al. [29]****	23	65	9:14	1: 2 >1: 21	NR	0: 18 1: 5	2 (8%)	8/23 (35%)	7 vs. 16	NR	4/23 (17.4%)	1.5 GBq	NR	3%	Embolization: 8/23 (34.8%) Surgery: 16/23 (69.6%) Chemotherapy: 12/23 (52.2%)	NR
Mosconi et al. [28]****	55	64	25:30	NR	5.6	0: 47 (85.5%) >0: 8 (14.5%)	NR	17/55 (30.9%)	27 vs. 28	NR	NR	1.29 GBq	NR	NR	Resection: 24/55 (43.6%) Embolization: 8/55 (14.5%) Chemotherapy: 23/55 (41.9%) Naive 23/55 (41.8%)	NR
Gangi et al. [41]	85	<70: 35 ≥70: 50	44:41	1: 52 >1: 33	NR	0: 35, 1: 22 2: 28	36/85 (42.4%)	NR	54 vs. 31	52 vs. 32	0	172.4 Gy	NR	5.5%	Chemotherapy: 24/85 (28.2%) Resection: 14/85 (16.5%) Radiation: 4/85 (4.7%)	NR

Table 1 (continued)

Study	Sample size	Age	Sex (female:male)	Tumor number	Tumor size, cm	ECOG	Metastasis	Cirrhosis	Unilobar vs. bilobar	Infiltrative vs. peripheral	Portal vein invasion	Dose	Tumor burden	Lung shunt fraction	Prior treatment	Concomitant chemotherapy
Haug et al. [30]****	26	64.3	11:15	NR	NR	NR	8/26 (31%)	NR	4 vs. 22	NR	NR	1.737 GBq	NR	NR	Chemotherapy: 17/26 (65%) Locoregional: 5/26 (20%) Resection: 8/26 (28%) Naïve: 6/26 (24%)	NR
Hoffman et al. [31]*****	33	65.2	15:18	1:10 >1:23	NR	0:17 1:7 2:9	8/33 (24.2%)	NR	12 vs. 21	21 vs. 12	NR	1.54 GBq	≤25%:25 >25%: 8	5.6%	Chemotherapy: 27/33 (81.8%) Resection: 12/33 (36.4%) TACE: 3/33 (9.1%) RFA: 2/33 (6.1%) Radiation: 1/33 (3%)	NR
Ibrahim et al. [34]*****	24	68	8:16	1:11 >1:13	NR	0:120 1:12 2:2	8/24 (33%)	1/24 (4%)	8 vs. 16	7 vs. 17	9 (38%)	105.1 Gy	≤25%: 20 25–50%: 3 50–75%: 1	NR	Chemotherapy: 7/24 (29%)	NR
Mouli et al. [33]*****	46	68	21:25	1:30 >1:16	NR	0:24 1:21 2:1	16/46 (35%)	NR	30 vs. 16	30 vs. 26	11/46 (24%)	NR	<25%: 36 25–50%: 8 >50%: 2	NR	Chemotherapy: 16/46 (35%) Resection: 5/46 (11%) RFA: 1/46 (2%) Transplant: 1/46 (2%)	NR
Jia et al. [35]	24	61.8	16:8	NR	NR	0:14 1:8	3/24 (12.5%)	NR	9 vs. 15	NR	NR	1.6 GBq	<25%: 7 25–50%: 8 >50%: 9	5.8%	Chemotherapy: 24/24 (100%)	0/24 (0%)
Kohler et al. [42]	46	62.5	27:19	NR	NR	≤2:46	14/46 (30.4%)	5/46 (10.9%)	17 vs. 29	NR	30/37 (81.1%)	1.74 GBq	<25%: 17 25–50%: 26 >50%: 3	<30%: 31 >30%: 6	Chemotherapy: 28/46 (93.3%) Radiation: 4/46 (13.3%) Immunotherapy: 1/46 (3.3%) Resection: 9/46 (30%) TACE: 1/46 (3.3%)	NR
Levillain et al. [43]	58	66	35:23	1:27 >1:31	NR	NR	NR	NR	25 vs. 33	NR	NR	NR	NR	NR	Resection: 30/58 (52%) Chemotherapy: 58/58 (100%)	NR
Raimier et al. [36]	21	69.5	9:12	1:12 >1:9	NR	1:3 2:16 3:2	3/21 (14.3%)	NR	17 vs. 4	11 versus 10	NR	NR	<25%: 8 25–50%: 13	NR	Naïve: 21/21 (100%)	0/21 (0%)
Saxena et al. [37]	25	≤57:14 >57:11	12:13	NR	NR	0:15 1:7 2:3	12/25 (48.0%)	NR	5 vs. 20	10 versus 15	0	1.76 GBq	<25%: 10 25–50%: 15	4.4%	Resection: 10/25 (40%) Chemotherapy: 18/25 (72%) RFA: 2/25 (8%) TACE: 2/25 (8%) Naïve: 6/25 (24%)	NR
Shaker et al. [45]	17	69.3	10:7	NR	NR	NR	6/17 (35.3%)	NR	NR	NR	NR	92.7 Gy	NR	NR	Resection: 4/17 (23.5%) Chemotherapy: 5/27 (18.5%)	0/17 (0%)
Soydal et al. [44]	16	55.4	8:8	1:6 >1:10	6.6	NR	5/16	NR	8 vs. 8	NR	NR	1.7 GBq	<25%: 4 25–50%: 8 >50%: 4	NR	Chemotherapy: 9/16 (56.3%) Resection: 2/16 (12.5%) TACE: 1/16 (6.3%) Naïve: 4/16 (25%)	NR
White et al. [38]	61	64	29:32	1–5: 31 (51%) 6–10: 9 (15%) >10: 13 (21%)	NR	0:32 1:23 2:2 Unknown: 4	22/58 (37.9%)	0	22 vs. 39	NR	NR	1.5 GBq (SIRS) 2.8 GBq (TheraSphere)	NR	NR	Chemotherapy: 56/61 (92%)	7/61 (11.5%)

GBq, gigabecquerel; Gy, gray; ECOG, Eastern Cooperative Oncology Group Status; NR, not reported; RFA, radiofrequency ablation; TACE, transarterial chemoembolization. Asterisks indicate studies using overlapping patient sample.

Fig. 1. Pooled RR and DCR. RR (a) and DCR (b) of SIRT. RR (c) and DCR (d) of EBRT. RR, response rate; DCR, disease control rate; SIRT, selective-internal radiation therapy; EBRT, external beam radiation therapy.

For patients who received EBRT, the MST ranged from 5.4 to 30 months. OS at 6 months, 1 year, 2 years, and 3 years were 67.2–98.7%, 30.4–87%, 0–61%, and 0–44%, respectively (Table 4). From the time of treatment, survival data of 272 patients were available from 10 studies (Fig. 2a). The MST was 13.6 (95% CI: 11.1–16.0) months from the time of first EBRT treatment. The cumulative OS rates at 6 months, 1 year, 2 years, and 3 years were 76.2% (70.7–80.8%), 49.8% (43.8–55.6%), 23.4%

(18.6–28.6%), and 9.5% (6.4–13.4%), respectively. Further differentiating by EBRT type (Fig. 2a), the MST of PT ($n = 98$), SBRT ($n = 43$), and CRT ($n = 106$) were 20.9 (95% CI: 5.2–13.6), 13.1 (95% CI: 10.0–21.1), and 10.0 (95% CI: 8.5–14.2) months, respectively. The 6-month, 1-year, 2-year, and 3-year OS of patients who underwent PT were 85.6 (95% CI: 77.0–91.2), 66.3% (95% CI: 55.9–74.8), 44.9% (95% CI: 34.4–54.9), and 31.4% (95% CI: 21.9–41.3), respectively, with an MST of 20.9 (95% CI:

Table 2. Baseline characteristics of patients who underwent RT

Study	Type	Sample size	Sex (female:male)	Tumor number	Tumor size, cm	ECOG	Metastasis	Cirrhosis	Unilobar vs. bilobar	Infiltrative vs. peripheral	Dose	Prior treatment	Concomitant chemotherapy
Ben-Josef et al. [56,70]	Conventional dose RT (photon)	46	20:26	NR	NR	NR	NR	NR	NR	NR	NR	Naive: 46/46 (100%)	NR
Chen et al. [54]*	Conventional dose RT (photon)	35	16 vs. 19	1: 26 >1: 9	7.7	NR	NR	NR	NR	12 vs. 23	50 Gy (delivered) BED cannot be derived	Naive: 35/35 (100%)	NR
Zeng et al. [55]*	Conventional dose RT (photon)	29	10:19	1: 5 >1: 24 >10: 9	<5 cm: 7 5–10 cm: 13	NR	NR	NR	29/29 (100%) Unilobar	NR	NR	Resection: 7/29 (24.1%)	0/29 (0%)
Cho et al. [51]	Conventional dose RT (photon)	64	Surgery group: 57 Non-surgery group: 59	1: 37 >1: 27	NR	0–1: 60 >1: 4	70.3%	NR	NR	18 vs. 46	BED: ≥55 Gy: 23/64 (35.9%) <55 Gy: 41/64 (64.1%)	Naive: 64/64 (100%)	64/64 (100%)
Hijazi et al. [57]	SBRT (photon)	6	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Hong et al. [65]**	Proton therapy	37	25:12	46	6	0: 15 1: 26	0	36/37 (97.3%)	NR	NR	58 GyRBE (delivered) BED: 80.45 Gy	Chemotherapy: 24/37 (64.9%) Resection: 1/37 (2.7%) Ablation: 1/37 (2.7%) TACE: 0 Naive: 14/37 (37.8%)	NR
Smart et al. [48]**	Hypofractionated RT (both photon and proton)	66	39:27	1: 46 2: 8 >2: 12	5.6	0: 29 1: 26 2: 9 3: 2	15/66 (22.7%)	6/66 (9.1%)	NR	NR	58.05 Gy (delivered) BED: 80.52 Gy	Chemotherapy: 28/66 (42.4%) Resection: 5/66 (7.6%)	NR
Yoon et al. [66]**	Mixed RT (both photon and proton)	6	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Tao et al. [52]**	Ablative dose RT (both photon and proton)	79	46:33	NR	7.9	0: 37 1: 37 2: 5	47/79 (59.5%)	NR	NR	44: 35	58.05 Gy (delivered) BED: 80.05 Gy	Chemotherapy: 70/79 (89%)	50/79 (63.3%)
Ibarra et al. [58]	SBRT	11	5:6	1: 9 >1: 2	5.4	NR	5/11 (45.5%)	NR	NR	NR	37.5 Gy (delivered) BED: 87.5 Gy	Resection: 50% RFA: 3/11 (27.3%) Chemotherapy: 5/11 (45.5%) TACE: 0	NR
Kasiyva et al. [59]	Carbon-ion radiation therapy	27	8:19	1: 22 >1: 5	4.3	0–1: 26 2: 1	0	NR	NR	NR	BED: 109.3 Gy	Naive: 21/27 (77.8%)	1/27 (3.7%)
Kozak et al. [60]	SBRT (photon)	25	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Kim et al. [53]	Conventional dose RT (both photon and proton)	25	6:19	1: 18 >1: 7	7.6	0: 10 1: 14 2: 1	11/25 (44.0%)	NR	NR	22: 3	44.7 Gy (delivered) BED cannot be derived	Naive: 25/25 (100%)	25/25 (100%)
Liu et al. [61]	SBRT (photon)	12	8:4	14	4.7	0: 5 1: 5 2: 2	NR	NR	NR	NR	BED: 92.94 Gy	Naive: 12/12 (100%)	8/12 (66.7%)
Ohkawa et al. [50]***	Proton therapy	20	9:11	1: 13 2: 7	5.0	0: 8 1: 7 2: 5	4/20 (20%)	NR	NR	NR	72.6 Gy (delivered) BED cannot be derived	Chemotherapy: 4/20 (20%) Resection: 3/20 (15%)	4/20 (20%)
Shimizu et al. [49]***	Proton therapy	42	15:22	1: 27 >1: 10	5.7	0: 12 1: 19 2: 6	NR	NR	NR	18 vs. 19	72.6 Gy (delivered) BED: 96.6 Gy	Naive: 42/42 (100%)	16/42 (38.1%)
Shen et al. [13]	SBRT (photon)	28	≤60: 11 >60: 17	1: 20 >1: 8	≤5: 6 5–10: 15 >10: 7	0: 16 1: 10 2: 2	0	8/28 (28.6%)	NR	6 vs. 22	BED: 85.5 Gy	Resection: 0 TACE: 8/28 (28.6%) Naive: 20/28 (71.4%)	NR
Sumiyoshi et al. [62]	Conventional dose RT (photon)	7	3:4	7	6.0	NR	NR	NR	NR	NR	50 Gy (total dose) BED: 60 Gy	Naive: 7/7 (100%)	7/7 (100%)
Tse et al. [63]	Conventional dose RT (photon)	10	57	NR	NR	NR	10/10 (100%)	0	NR	NR	32.5 Gy (delivered) BED: 50.1 Gy	Naive: 5/10 (50%) Chemotherapy: 4/10 (40%) Resection: 1/10 (10%)	0/10 (0%)
Weiner et al. [64]	SBRT (photon)	12	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

NR, not reported; RFA, radiofrequency ablation; RT, radiation therapy; SBRT, stereotactic beam radiation therapy; TACE, transarterial chemotherapy; ECOG, Eastern Cooperative Oncology Group Status. Asterisks indicate studies using overlapping patient sample.

Table 3. Radiographical and survival outcomes of included studies on radioembolization

Study	Criteria	Radiological Outcome	MST, months	OS
Akinwande et al. [20]	mRECIST	CR: 1/19 PR: 0 SD: 11/19 PD: 7/19	NA	NA
Beuzit et al. [23]*	RECIST (also reported Choi)	CR: 0 PR: 6/45 SD: 32/45 PD: 7/45	19.0	6 mo: NA 1 yr: 54.0% 2 yr: 40.7% 3 yr: NA
Edeline et al. [14]*	RECIST	Not shown	Not shown	Not shown
Edeline et al. [24]*	RECIST	Not shown	Not shown	Not shown
Manceau et al. [21]*	EASL	Not shown	Not shown	Not shown
Rayar et al. [47]*	NA	NA	Not shown	NA
Riby et al. [46]*	RECIST	Not shown	Not shown	Not shown
Camacho et al. [39]**	RECIST (also reported PERCIST)	Not shown	Not shown	Not shown
Rafi et al. [22]**	RECIST	CR: 0 PR: 2/19 SD: 13/19 PD: 4/19	Not shown	6 mo: 68.0% 1 yr: 48.5% 2 yr: 9.5% 3 yr: NA
Xing et al. [40]**	NA	NA	LSF <10%: 26.1 LSF ≥10%: 16.1	NA
Buettner et al. [1, 32]	RECIST	PR: 7/96 SD: 63/96 PD: 26/96	11	6 mo: 68.9% 1 yr: 44% 2 yr: 19.8% 3 yr: 4%
Filippi et al. [25]***	PERCIST	CR:0 PR: 14/17 SD: 3/17 PD: 0	Not shown	Not shown
Filippi et al. [27]***	PERCIST	Not shown	Not shown	Not shown
Filippi et al. [26]***	NA	NA	12.5	6 mo: 75% 1 yr: 40% 2 yr: 5% 3 yr: NA
Mosconi et al. [29]****	RECIST (also reported mRECIST and EASL)	Not shown	Not shown	Not shown
Mosconi et al. [28]****	RECIST	CR: 4/53 PR: 26/53 SD: 19/53 PD: 4/53	16.7	6 mo: 90.8% 1 yr: 59.4% 2 yr: 31.8% 3 yr: NA
Gangi et al. [41]	RECIST	CR: 0 PR: 5/81 SD: 52/81 PD:24/81	12	6 mo: 70% 1 yr: 49% 2 yr: 38% 3 yr: NA
Haug et al. [30]*****	RECIST	Not shown	Not shown	Not shown

Table 3 (continued)

Study	Criteria	Radiological Outcome	MST, months	OS
Hoffman et al. [31]*****	RECIST	CR: 0 PR: 12/34 SD: 17/34 PD: 5/34	22	6 mo: 84.0% 1 yr: 57.3% 2 yr: 42.0% 3 yr: 12.8%
Mouli et al. [33]*****	WHO (also reported EASL)	CR: 0 PR: 11/45 SD: 33/45 PD: 1/45	10	6 mo: 69.2% 1 yr: 43.8% 2 yr: 27.7% 3 yr: 12.9%
Ibrahim et al. [34]*****	WHO	Not shown	Not shown	Not shown
Jia et al. [35]	mRECIST	CR: 0 PR: 8/22 SD: 10/22 PD: 4/22	9.0	6 mo: 69.9% 1 yr: 32.6% 2 yr: 20.4% 3 yr: NA
Kohler et al. [42]	RECIST	CR: 0 PR: 16/35 SD: 7/35 PD: 12/35	9.5	6 mo: 65.2% 1 yr: 40.6% 2 yr: 8.5% 3 yr: 8.5%
Levillain et al. [43]	NA	NA	6.3	6 mo: 66.9% 1 yr: 40.0% 2 yr: 22.0% 3 yr: 11.2%
Reimer et al. [36]	RECIST	CR: 0 PR: 1/21 SD: 9/21 PD: 11/21	15	6 mo: 100% 1 yr: 93.7% 2 yr: 68.6% 3 yr: 46.2%
Saxena et al. [37]	RECIST	CR: 0 PR: 6/22 SD: 11/22 PD: 5/22	20.4	6 mo: 56% 1 yr: 40% 2 yr: 27% 3 yr: 13%
Shaker et al. [45]	NA	NA	33.6	NA
Soydal et al. [44]	NA	NA	9.8	6 mo: 56.3% 1 yr: 32.8% 2 yr: 10.9% 3 yr: NA
White et al. [38]	NA	NA	13.9	6 mo: 68.7% 1 yr: 37.4% 2 yr: 7.5% 3 yr: NA

CR, complete response; EASL, European Association for the Study of the Liver; MST, median survival time; NA, not reported by original study; Not shown, data were not displayed in the table because the outcome was reported by another larger study with overlapping patient sample; OS, overall survival; PD, progressive disease; PERCIST, positron emission tomography response criteria in solid tumors; PR, partial response; RECIST, response evaluation criteria in solid tumors; mRECIST, modified RECIST; SD, stable disease; WHO, World Health Organization. Asterisks indicate studies using overlapping patient sample.

Fig. 2. Kaplan-Meier survival curve of patients who underwent SIRT or EBRT. **a** Survival from initial treatment. **b** Survival from initial diagnosis. **c** Survival among treatment-naïve patients who received SIRT or external radiation therapy. CRT, conventional dose radiation therapy (photon); PT, proton beam radiation therapy; SBRT, stereotactic-body radiation therapy; SIRT, selective-internal radiation therapy; EBRT, external beam radiation therapy; OS, overall survival. Mixed: EBRT studies including patients who received more than one type of modality from CRT, SBRT, and PT.

14.4–25) months. The SBRT group had OS rates of 85.4% (70.3–93.1), 56.1% (39.7–69.6), 34.2% (20.1–48.8), and 15.4% (6.2–28.3) at 6 months, 1 year, 2 years, and 3 years, whereas CRT group had OS rates of 74.3% (64.8–81.6), 47.4% (37.6–56.5), 22.1% (14.7–30.5), and 12.8% (7.2–20.0), respectively.

From the time of iCCA diagnosis (Fig. 2b) [14, 24, 25, 35, 36, 39, 41, 48, 49, 51–54, 62], the MST of SIRT ($n = 176$) and EBRT ($n = 308$) were 25 (95% CI: 20.6–28.5) versus 18.1 (95% CI: 9.3–13.6) months, with OS rates of 74.3% (95% CI: 64.8–81.6%), 85.0% (95% CI: 78.7–89.6%),

54.2% (95% CI: 46.2–61.6%), and 37.0% (95% CI: 29.4–44.5%) at 6, 12, 24, and 36 months, respectively, versus 84.3% (95% CI: 79.7–87.9%), 64.9% (95% CI: 59.2–70.0%), 38.2% (95% CI: 33.6–44.8%), and 25.7% (95% CI: 20.8–30.8%).

Among patients who were treatment-naïve [24, 25, 49, 51, 53, 54, 62] (Fig. 2c), the MST for SIRT ($n = 58$) and EBRT ($n = 163$) were 36.1 (95% CI: 20.6–39.5) and 11.0 (95% CI: 9.3–13.6) months, respectively. The OS rates of SIRT were 96.4% (95% CI: 86.2–99.1%), 88.6% (95% CI: 76.3–94.7%), 66.3% (95% CI: 51.0–77.8%), and 56.0%

Table 4. Radiographical and survival outcomes of included studies on RT

Study	Criteria	Radiological outcome	MST, months	OS
Shimizu et al. [49]*	RECIST	3 mo DCR: 36/37	15.0	6 mo: 83.6% 1 yr: 60.3% 2 yr: 41.4% 3 yr: 31.0%
Ohkawa et al. [50]*	Not shown	Not shown	Not shown	Not shown
Shen et al. [13]	mRECIST	CR: 3/28 (10.7%) PR: 10/28 (35.7%) SD: 12/28 (42.9%) PD: 3/28 (10.7%)	15.0	6 mo: 89.3% 1 yr: 57.1% 2 yr: 32.1% 3 yr: 10.7%
Kim et al. [53]	RECIST	CR: 0 PR: 1/25 (4.0%) SD: 13/25 (52.0%) PD: 11/25 (44.0%)	9.3	6 mo: 67.7% 1 yr: 30.4% 2 yr: 12.5% 3 yr: NA
Chen et al. [54]**	EASL	CR: 3/35 (8.6%) PR: 10/35 (28.5%) SD: 17/35 (48.6%) PD: 5/35 (14.3%)	5.4	6 mo: 76.5% 1 yr: 38.5% 2 yr: 9.6% 3 yr: NA
Zeng et al. [55]**	Not shown	Not shown	Not shown	Not shown
Hijazi et al. [57]	RECIST	3 mo DCR: 3/4 (75%)	10	6 mo: 79.9% 1 yr: 79.9% 2 yr: 0% 3 yr: 0%
Ibarra et al. [58]	RECIST	CR: 1/9 (11.1%) PR: 2/9 (22.2%) SD: 2/9 (22.2%) PD: 4/9 (44.4%)	11	6 mo: 75% 1 yr: 45% 2 yr: NA 3 yr: NA
Sumiyoshi et al. [62]	RECIST	CR: 0 PR: 4/7 (57.1%) SD: 1/7 (14.3%) PD: 2/7 (28.6%)	Needs calculation	6 mo: 80% 1 yr: 40% 2 yr: 20% 3 yr: 20%
Kasuya et al. [59]	Not shown	Not shown	23.8	6 mo: 96.3% 1 yr: 77.7% 2 yr: 53.2% 3 yr: 36.9%
Smart et al. [48]***	NA	NA	Not shown	6 mo: 90.8% 1 yr: 79.1% 2 yr: 58% 3 yr: 30.2%
Hong et al. [65]***	RECIST	3 mo DCR: 36/36	Not shown	Not shown
Yoon et al. [66]***	RECIST	Not shown	Not shown	Not shown
Tao et al. [52]***	NA	NA	30	6 mo: 98.7% 1 yr: 87% 2 yr: 61% 3 yr: 44%
Ben-Josef et al. [56, 70]	NA	CR: 4/33 (12.1%) PR: 8/33 (24.2%) SD: 20/33 (60.6%) PD: 1/33 (3.0%)	NA	NA

Table 4 (continued)

Study	Criteria	Radiological outcome	MST, months	OS
Cho et al. [51]	RECIST	CR: 0 PR: 16/56 (25%) SD: NA PD: NA	10	6 mo: 67.2% 1 yr: 48.4% 2 yr: 25% 3 yr: 15.8%
Kozak et al. [60]	NA	NA	23	6 mo: 95.5% 1 yr: 76.2% 2 yr: 47.3% 3 yr: 34.1%
Liu et al. [61]	RECIST	CR: 1/12 (8.3%) PR: 6/12 (50.0%) SD: 3/12 (25.0%) PD: 2/12 (16.7%)	NA	NA
Tse et al. [63]	RECIST	NA	15	6 mo: 79.6% 1 yr: 58.2% 2 yr: 28.4% 3 yr: NA
Weiner et al. [64]	EASL	CR: 1/12 (8.3%) PR: 3/12 (25%) SD: NA PD: NA	NA	NA

CR, complete response; DCR, disease control rate; EASL, European Association for the Study of the Liver; MST, median survival time; NA, not reported by original study; Not shown, data were not displayed in the table because the outcome was reported by another larger study with overlapping patient sample; OS, overall survival; PD, progressive disease; PERCIST, positron emission tomography response criteria in solid tumors; PR, partial response; RECIST, response evaluation criteria in solid tumors; mRECIST, modified RECIST; SD, stable disease; WHO, World Health Organization. Asterisks indicate studies using overlapping patient sample.

Table 5. Downstaging to surgery

Study	Intervention	Surgery	Treatment-naïve patients who received surgery
Buettner et al. [1, 32]	SIRT	5/115 (4.3%)	1/14
Beuzit et al. [23]*	SIRT	9/45 (20%)	NS
Edeline et al. [14]*	SIRT	11/24 (46%)	NS
Edeline et al. [24]*	SIRT	9/41 (22.0%)	NS
Manceau et al. [21]*	SIRT	17/35 (49%)	17/35
Rayar et al. [47]*	SIRT	Downstaging-only: 8 pts	NS
Riby et al. [46]*	SIRT	Downstaging-only: 19 pts	NS
Mouli et al. [33]**	SIRT	5/46 (11%)	5/18
Ibrahim et al. [34]**	SIRT	2/24 (8.3%)	NS
Saxena et al. [37]	SIRT	1/25 (4%)	1/6
Shaker et al. [45]	SIRT	1/17 (5.9%)	1/9
Cho et al. [51]	EBRT	8/64 (12.5%)	8/64
Sumiyoshi et al. [62]	EBRT	5/7 (71.4%)	5/7

SIRT, selective-internal radiation therapy; EBRT, external body radiation therapy; NS, not shown due to overlapping patients. Asterisks indicate studies using overlapping patient sample.

Table 6. Pooled post-procedural complications after SIRT or EBRT

Complication	SIRT	EBRT
Ulcer	2/198 (1.0%)	2/388 (0.5%)
Nausea	3/190 (1.6%)	2/276 (0.7%)
Vomiting	1/181 (0.6%)	2/263 (0.7%)
Anorexia	14/238 (5.9%)	0/24 (0%)
Abdominal pain	9/130 (6.9%)	11/492 (2.2%)
Anemia	1/154 (0.6%)	8/105 (7.5%)
Neutropenia	10/154 (6.5%)	21/191 (11.0%)
Thrombocytopenia	12/164 (7.3%)	10/167 (6.0%)
ALP	2/127 (1.6%)	2/238 (0.8%)
AST	1/147 (0.7%)	3/297 (1.0%)
ALT	3/147 (2.0%)	0/288 (0%)
Bilirubin	9/174 (5.2%)	8/381 (2.1%)
Albumin	5/38 (13.2%)	5/151 (3.3%)

SIRT, selective-internal radiation therapy; EBRT, external body radiation therapy.

(95% CI: 40.5–69.0) at 6 months, 1 year, 2 years, and 3 years, respectively, compared with those of EBRT: 74.7% (95% CI: 67.3–80.7%), 47.0% (95% CI: 39.2–54.5%), 23.3% (95% CI: 17.0–30.1%), and 13.7% (95% CI: 8.9–19.6%). By subgroups of EBRT, the MST of PT ($n = 32$), and CRT ($n = 106$) were 12.0 (95% CI: 9.0–25.0) and 10.0 (95% CI: 8.5–14.2) months, respectively. No survival data regarding SBRT as the first-line treatment could be pooled.

Downstaging to Surgery

Nine studies of SIRT reported the number of initially unresectable iCCA that were eventually resected after neoadjuvant therapy (Table 5). The proportion of patients who eventually received surgery ranged from 4 to 49%, excluding studies that solely focused on downstaged patients. One patient was downstaged to transplant [34]. By contrast, 12.5–71.4% patients who underwent EBRT were downstaged to surgical resection; these patients received conventional dose 3 DCRT or IMRT. Among patients who were treatment-naïve, a cumulative of 30.5% (25/82) and 18.3% (13/71) of patients who received SIRT and EBRT were downstaged to surgery. Patient-level survival data were available in 26 patients (Fig. 3). Neither group reached MST, with a 1-year OS of 90.1% (95% CI: 67.7–97.6%) and 51.5% (95% CI: 30.8–81.8%) in SIRT and EBRT groups, respectively.

Fig. 3. OS rates among patients who were downstaged to surgery after SIRT or EBRT. SIRT, selective-internal radiation therapy; EBRT, external beam radiation therapy; OS, overall survival.

Toxicity

The pooled severe complications are listed in Table 6, with the specific event from each study listed in online suppl. Tables 3.1 and 3.2. Compared to the SIRT group, patients who underwent EBRT had a higher rate of severe complications including: peptic ulcer (1 vs. 0.5%), nausea (1.6 vs. 0.7%), anorexia (6.0% vs. 0%), abdominal pain (6.9 vs. 2.2%), thrombocytopenia (7.3 vs. 6.0%), hypoalbuminemia (13.2 vs. 3.3%), and elevations in liver enzymes – ALP (1.6 vs. 0.8%), ALT (2% vs. 0%), and bilirubin (5.2 vs. 2.1%). SIRT had a higher rate of major complication in anemia (7.5 vs. 0.6%), neutropenia (11.0 vs. 6.5%), and AST elevation (1.0% vs. 0.7%). Radiation-induced dermatitis only occurred in EBRT patients [48, 49, 53], with a frequency from 28 to 88%, but not the SIRT patients. No radiation-induced pneumonitis was observed.

Discussion

Both SIRT and EBRT are acceptable treatments for unresectable iCCA in a variety of clinical scenarios including first-line therapy, chemorefractory tumors, recurrence of cancer, as combination therapy (in conjunction with chemotherapy), or neoadjuvant therapy [1, 11]. A head-to-head comparison of EBRT versus SIRT under each specific clinical setting remains difficult, as most published literature on this topic includes a widely heterogeneous patient population. Limited evidence is avail-

able regarding the comparative efficacy of SIRT versus EBRT in treating liver malignancies. Based on the National Cancer Database, Oladeru et al. [67] indicated that RE and SBRT resulted in similar survival benefits in patients with unresectable HCC, whereas Sebastian et al. [17] suggested that the latter was superior to both SIRT and conventional dose chemoradiotherapy in cholangiocarcinoma. In a meta-analysis of 37 studies on HCC with PVI, OS rates among 3D CRT, SIRT, and SBRT were comparable [68]. None of the available evidence including the studies mentioned above focused on SIRT versus EBRT as the first-line treatment, which might otherwise be prone to selection bias. Likewise, in the present study, the prespecified primary end point of OS between treatment arms proved to be difficult due to different baseline conditions among the SIRT and EBRT groups, as the former was often implemented as salvage rather than primary treatment (Tables 1, 2). To account for this, the present study reported OS of treatment-naïve patients, in addition to from the time of radiation treatment and iCCA diagnosis. Among treatment-naïve patients (Fig. 2e, f), the MST for SIRT and EBRT were 36.1 (95% CI: 20.6–39.5) and 11.0 (95% CI: 9.3–13.6) months, respectively; the MST of PT and CRT were 12.0 (95% CI: 9.0–25.0) and 10.0 (95% CI: 8.5–14.2) months, respectively. Though the survival of SBRT among treatment-naïve patients was unknown, the OS from initial SBRT was 13.1 (95% CI: 10.0–21.1) months. While the baseline heterogeneity between 2 groups prevents high-quality comparative analysis, the present study offers baseline survival outcomes for future RCTs comparing these 2 treatment modalities.

For advanced iCCA, the National Comprehensive Cancer Network guideline recommends cisplatin-gemcitabine chemotherapy as first-line treatment [69]. Among included studies of the present meta-analysis, 60.1% (514/855) of SIRT and 29.7% (135/454) EBRT patients received prior chemotherapy, while the percentage of patients who received concomitant chemotherapy were 43.4% (151/348) and 55.6% (175/315), respectively (Tables 1, 2). Among treatment-naïve subgroup analysis, 60.3% (35/58) and 68.7% (112/163) patients received SIRT and EBRT combined with chemotherapy (Tables 1, 2). Lamarca et al. [85] performed a post hoc analysis of 66 iCCA patients who were treated with first-line cisplatin-gemcitabine chemotherapy in Advanced Biliary Tract Cancer-01, -02, and -03 studies. Among 51.5% (34/66) patients with the liver-only disease, the MST was 16.7 (95% CI: 8.7–22.2) months, compared with the 2 recently published prospective multicenter clinical trials from the present meta-analysis, reporting MST of 22 and 22.5

months for iCCA patients who received SIRT and high-dose hypofractionated PT, respectively. Patients with localized disease burden demonstrated longer OS than those with extrahepatic metastasis, which did not reach statistical significance (HR = 0.65, $p = 0.16$) due to underpowering. The addition of locoregional therapy, such as EBRT and SIRT on top of chemotherapy could potentially be beneficial in this patient group if surgery were contraindicated.

The baseline heterogeneity between SIRT and EBRT groups was difficult to adjust due to the nature of study-level data. Reported predictors of survival among iCCA patients receiving radiation therapy include lesion number [33], lobar distribution [42], history of surgery [42], BED [52], adjuvant chemotherapy administration [49], and the presence of jaundice [49]. These variables can serve as a reference for future RCT design and stratification. One additional difficulty in comparing EBRT versus SIRT is standardizing effective radiation doses between 2 modalities. A higher radiation dose correlates positively with the survival [70]. Theoretically, SIRT can deliver higher concentrated radiation doses to tumor than EBRT with a sustained radiation for approximately 2 weeks post-procedurally [71]. While SIRT studies often report in GBy, EBRT reports total delivered doses and BEDs (Tables 1, 2). BED of SIRT has been calculated with the consideration of time factors, despite downsides such as single-photon emission computed tomography being less accurate than PET/CT [72, 73]. The development of a conversion algorithm may be needed to characterize the relationship of radiation dosage and clinical outcomes in future studies comparing EBRT and SIRT.

A variety of imaging criteria were adopted to evaluate posttreatment objective radiographical response in the present meta-analysis: RECIST, mRECIST, PERCIST, WHO, and EASL (Fig. 1). Most included studies measured radiologic response according to the RECIST criteria. The RR and DCR seemed to be higher in patients who received EBRT than SIRT: 22% (95% CI: 10–37%) versus 31% (95% CI: 12–54%) and 75% (95% CI: 65–84%) versus 83% (95% CI: 61–98%). Yet, RECIST has a questionable reliability in the evaluation of locoregional therapy (including RE) responses in hepatic malignancies [74–77]. Because Y-90 RE induced tumor necrosis often accompanied peripheral edema, the objective radiographical response could be underestimated and may not necessarily correlate with survival [78]. Camacho et al. [39] retrospectively evaluated 9 patients treated with Y-90 radioembolization and showed that RECIST poorly correlated with OS. Likewise, in a retrospective cohort of 45 patients who

received SIRT for iCCA, Beuzit et al. [23] did not observe significant survival difference based on RECIST, but Choi responders correlated with prolonged survival difference. Few studies implemented the PERCIST criteria, which provide a more accurate assessment of tumor metabolic activity than RECIST [25, 30]. Further, the posttreatment imaging follow-up intervals varied among studies. While most studies measured the objective radiological RR at 3-month post embolization [23, 31, 41], some only reported these outcomes at 1-month follow-up or the best responses achieved [28, 51, 56]. As such, standardization of posttreatment objective radiological response evaluation is needed between interventional radiologists and radiation oncologists to allow future comparative analysis.

As the definitive treatment of iCCA, surgical resection is determined by an interplay of tumor number, vascular/ductal invasion, the presence of extrahepatic disease, and hepatic functional reserve [79–82]. The present study suggested that both SIRT and EBRT effectively reduced tumor burden and could downstage initially unresectable tumors to surgery (Fig. 3), despite small sizes ($n = 13$ in each group). Of note, both SIRT and EBRT could only be implemented to bridge surgery when tumor size was the limiting factor. Among the 8 patients who were downstaged to surgery in the study of Rayar et al. [47], the initial unresectability was due to tumoral involvement of the hepatic vein and portal vein. In the study by Mouli et al. [33], all 13 initially “downstageable” cases were solitary lesions without cirrhosis, and the 5 downstaged patients were ECOG 0 without portal vascular invasion. Further, in the 9 patients of Edeline et al. [24], tumor regression was achieved in tumors that initially invaded hepatic and portal veins, allowing surgical hepatectomy. Interestingly, it was also observed that the liver remnant volume also increased after SIRT, suggesting that SIRT promoted liver hypertrophy and enhanced hepatic function reserve [47], which may broaden patient’s surgical candidacy and warrant validation from future studies. As for EBRT, in the study of Sumiyoshi et al. [62], the reasons of unresectability included 4 extrahepatic perineural invasions and 3 vascular invasions to hepatic vein and IVC. Tumor size reduction was observed in all cases; 5 eventually received surgery, while 2 developed extrahepatic metastases and thus lost candidacy. Among the 8 downstaged patients in the study of Cho et al. [51], 3 presented with major vessel invasion; tumor regression was observed in all cases after EBRT. Despite the pooled successful downstage rate among treatment-naïve patients being lower in the SIRT group (30.5 vs. 18.3%), such analysis should be interpreted with caution because the proportion of patients who were “downstageable” was unknown. For example, patients who

presented with extrahepatic metastases, had poor baseline neurofunctional status, and received treatment with a palliative intent should not be considered in the baseline treatment group in such analyses. This is particularly relevant for EBRT, where only patients receiving curative radiation dosages should be considered. Thus, whether SIRT is truly superior to EBRT in downstaging iCCA remains to be answered by high-quality comparative studies.

The overall toxicity profile from included studies was low. Clinical complications, such as severe peptic ulcer disease, nausea, anorexia, and abdominal pain occurred more frequently in the EBRT cohort (Table 6). In addition, radiation-related dermatitis was exclusive to EBRT. All neutropenia, anemia, and thrombocytopenia cases among the SIRT group occurred in 1 study that combined SIRT with chemotherapy, suggesting enhanced bone marrow-related toxicity when these 2 modalities were administered simultaneously [24, 83]. Two cases of radiation-induced liver disease (RILD) occurred in the EBRT arm: one case resolved with corticosteroids and the other resulted in death [48, 54]. In comparison, 2/5 RILD cases in the SIRT group were considered life-threatening, though specific details were not provided by the original study [32, 38]. While PT should reduce complications observed with photon-based RT owing to Bragg peak [84], subgroup analyses based on RT subtypes were not possible for the rare incidence in the present study.

The present meta-analysis should be interpreted with several caveats. First, each treatment arm was pooled independently from single-arm studies. Because of the variations in data reporting, the baseline characteristics of each treatment group could not be pooled and compared. For example, technical variances among institutions and additional patient-specific characteristic might also contribute to underlying heterogeneity. Such heterogeneity prohibits a head-to-head comparison between these 2 treatment modalities. Second, although individual survival data was retrieved from original studies, several studies did not label “tick” (censored data). In addition, some studies had overlapping ticks, and therefore not every patient could be mapped. The decision to exclude these studies inevitably led to the loss of a large proportion of available data. However, excluding censored data would underestimate the true survival rate. Third, stratification based on curative versus palliative intent was not performed, as the original studies rarely provided outcomes with such categorizations. Finally, many EBRT studies including iCCA patients were excluded as these studies also included hilar and distal CCA, which could certainly lead to the present study being underpowered.

Robust evidence has demonstrated that the genetics, molecular progression, and clinical behaviors of these 3 subgroups of CCA are distinct from one another and therefore should be treated as distinct entities.

Conclusion

The present study reviewed the available evidence of EBRT and SIRT in the management of unresectable iCCA. Both treatments demonstrated efficacy with acceptable toxicity profiles and can serve as bridging treatment to surgery. Survival benefits varied among different subtypes of EBRT. There was no consensus regarding the most reliable radiographic criteria comparing the treatment efficacies of SIRT and EBRT. Patients with iCCA who underwent SIRT versus EBRT were heterogeneous in treatment approach and disease severity which limited the ability to make broad conclusions. As such, given the noncomparative nature of each included study, future prospective, multicenter randomized controlled trials are needed to determine superiority of specific radiotherapies in iCCA.

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Statement of Ethics

The authors have no ethical conflicts to disclose. The research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. Ethical review and approval was not required as the study is based exclusively on published literature.

Conflict of Interest Statement

The authors have no conflict of interest to declare.

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