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ORIGINAL RESEARCH

A pooled analysis of transarterial radioembolization with yttrium-90 microspheres for the treatment of unresectable intrahepatic cholangiocarcinoma

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Purpose: The aim of this pooled analysis was to evaluate the clinical efficacy and safety of transarterial radioembolization (TARE) with yttrium-90 (^{90}Y) microspheres for the treatment of unresectable intrahepatic cholangiocarcinoma (ICC).

Methods: We searched the Cochrane Library, Embase, PubMed, SCI with the English language from inception to October 2018. A pooled analysis was conducted using Stata software.

Results: There were 16 eligible studies included in this pooled analysis. The pooled median overall survival (OS) from 12 studies was 14.3 (95% CI: 11.9–17.1) months. Based on Response Evaluation Criteria in Solid Tumors (RECIST), no complete response was reported, and the median of partial response, stable disease and progressive disease were 11.5% (range: 4.8–35.3%), 61.5% (range: 42.9–81.3%) and 22.7% (range: 12.5–52.4%) respectively. The pooled disease control rate (DCR) from nine studies was 77.2% (95% CI: 70.2–84.2%). According to the type of microspheres, subgroup analysis was performed, the median OS in the glass microspheres group was 14.0 (95% CI: 9.1–21.4) months, and 14.3 (95% CI: 11.5–17.8) months in the resin microspheres group. The DCR was 77.3% (95% CI: 63.5–91.1%) and 77.4% (95% CI: 66.8–87.9%) in the glass and resin microspheres groups respectively. Most of the side effects reported in the included studies were mild and did not require intervention.

Conclusion: TARE with ^{90}Y microspheres is safe and effective for patients with unresectable ICC with acceptable side effects. And it seems that the type of microsphere has no influence on therapeutic efficacy.

Keywords: transarterial radioembolization, yttrium-90 microspheres, intrahepatic cholangiocarcinoma, pooled analysis

Introduction

Intrahepatic cholangiocarcinoma (ICC) is a highly invasive malignancy of the biliary tract with high mortality due to its infiltrative nature, propensity for advanced disease presentation and resistance to chemotherapy.[1,2] From diagnosis, the median overall survival (OS) of ICC without treatment is about 4.5 months. Surgical resection may be the only potentially curative treatment, however, only 30–40% of ICC patients are the surgical candidate when the diagnosis is first confirmed.[3,4] Systemic chemotherapy with cisplatin plus gemcitabine is also limited

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by poor response rates.[5,6] Transarterial radioembolization (TARE) with yttrium-90 (^{90}Y)-labeled glass or resin microspheres are being used increasingly in primary and secondary liver malignancies, which provides an advantage to the median OS with good tolerance.[7,8] Al-Adra et al[9] reviewed 12 studies regarding TARE with ^{90}Y microspheres for the treatment of unresectable ICC in 2014; there are emerging studies on TARE with ^{90}Y microspheres for the treatment of ICC, so it is necessary to further systematically evaluate the outcomes of TARE with ^{90}Y microspheres in these patients. The aim of this pooled analysis was to comprehensively evaluate the therapeutic efficacy and safety of TARE with ^{90}Y microspheres for the treatment of unresectable ICC.

Material and methods

Search strategy

We searched the Cochrane Library, Embase, PubMed, SCI with English language from inception to October 2018. Relevant documents were supplemented by references of retrieved articles. The terms we used to search were related to intrahepatic cholangiocarcinoma, intrahepatic bile duct carcinoma, cholangiocellular carcinoma, neoplasms of the biliary tract, cholangiohepatoma, yttrium-90, Y90, ^{90}Y, SIR-Spheres, TheraSphere, radiation lobectomy.

Inclusion and exclusion criteria

1. Clinical trials or studies
2. Studies that described TARE with ^{90}Y microspheres in the treatment of unresectable ICC

Exclusion criteria

1. Review articles, animal studies, abstracts, case reports
2. Duplicated clinical studies
3. Studies with fewer than 10 cases

The quality of the studies was independently evaluated by two reviewers based on the Downs and Black quality assessment checklist.[10]

Data extraction

Two authors extracted the data and a third one resolved any disagreements. The extracted data included details of type of researches (prospective or retrospective cohort), number of patients, age, sex, Eastern Cooperative Oncology Group (ECOG) score, extrahepatic metastases, pre- and postchemotherapy, type of microspheres, dosimetric calculation, follow-up time, median OS, 1-year survival, evaluation criteria, tumor response, side effects (eg clinical toxicities such as fatigue, abdominal pain, nausea, and biochemical toxicities such as decreased albumin, elevated bilirubin, alkaline phosphatase, etc).

Statistical analysis

Only median OS and disease control rate (DCR) were pooled analysis by Stata 11.0 (StataCorp. 2009. Stata Statistical Software: Release 11. College Station, TX: StataCorp LP.), while other outcomes were analyzed in descriptive statistics. The I^2 measure was used to show the inconsistency between studies. An Egger test was used to assess publication bias, and Metaninf was used for sensitivity analysis, a two-sided $P<0.05$ was regarded as significant.

Results

According to the inclusion and exclusion criteria, 16 eligible studies[11–26] were identified that reported the TARE with ^{90}Y microspheres for unresectable ICC (Figure 1). Five prospective and 11 retrospective studies were included. There were 472 patients included in this pooled analysis. Patient characteristics were presented in Table 1. Extrahepatic metastases were observed in a median of 48.7% (range: 8.7–57.9%). A median of 71.9% (range: 0.0–100.0%) patients received systemic chemotherapy before TARE with ^{90}Y microspheres, and a median of 12.3% (range: 7.1–28.0%) received postoperative chemotherapy.

Table 2 summarized information about the therapeutic outcomes of TARE with ^{90}Y microspheres for ICC. The pooled median OS from 12 studies was 14.3 (95%CI: 11.9–17.1) months (Figure 2). The tumor response at 3 months after TARE with ^{90}Y microspheres was evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST), no complete response was reported, and the median of partial response, stable disease, progressive disease was 11.5% (range: 4.8–35.3%), 61.5% (range: 42.9–81.3%), 22.7% (range: 12.5–52.4%) respectively. The pooled DCR from available studies was 77.2% (95%CI: 70.2–84.2%) (Figure 3). Subgroup analysis was conducted by microspheres type, the median OS in the glass microspheres group was 14.0 (95%CI: 9.1–21.4) months, and 14.3 (95% CI: 11.5–17.8) months in the resin microspheres group. The

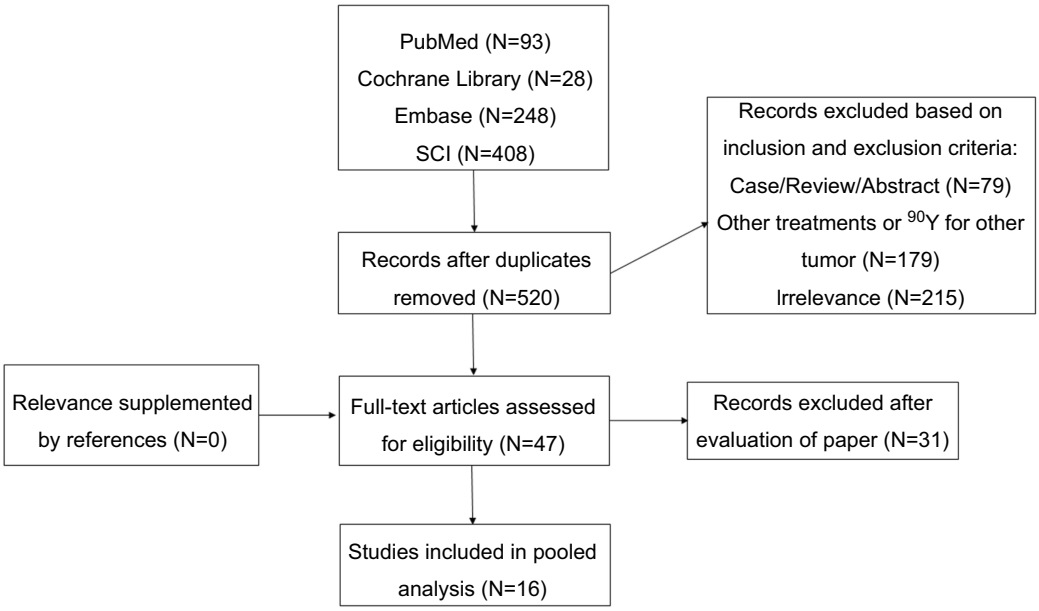

Figure 1 A flowchart of study identification and selection.

DCR was 77.3% (95%CI: 63.5–91.1%) and 77.4% (95%CI: 66.8–87.9%) in the glass and resin microspheres group respectively. There were six studies reporting 1-year survival rate with a median of 51.5% (range: 32.6–67.9%).

Side effects and the proportion of grade III–IV toxicities were listed in Table 3. Clinical toxicities mainly included fatigue (median: 31.7%; range: 0.0–87.5%), anorexia (median: 10.0%; range: 0.0–79.2%), abdominal pain (median: 30.0%; range: 0.0–85.0%), nausea (median: 16.0%; range: 0.0–62.5%), vomiting (median: 9.0%; range: 0.0–27.0%), ascites (median: 10.5%; range: 0.0–21.7%). Biochemical toxicities were decreased albumin (median: 2.0%; range: 0.0–9.0%), elevated bilirubin (median: 5.7%; range: 0.0–70.0%), elevated alkaline phosphatase (median: 1.7%; range: 0.0–46.0%). The incidence of gastroduodenal ulceration was a median of 4.0% (range: 0.0–5.0%) in 5 studies reporting side effects. A median of 7.8% (range: 0.0–25.0%) grade III–IV toxicities (including gastroduodenal ulceration) was reported in 10 studies.

Mild and moderate heterogeneity was shown in pooled median OS and DCR. These estimates were robust in the sensitivity analysis. No significant publication bias was identified in pooled analysis.

Discussion

The pooled analysis showed that TARE with ^{90}Y microspheres can be an effective treatment for unresectable ICC with a pooled median OS of 14.3 (95%CI: 12.0–17.1) months. According to RECIST, the pooled DCR was 77.2% (95%CI: 70.2–84.2%). Subgroup analysis was conducted by microsphere type, it seems that there were similar median OS and DCR in the glass and resin microspheres group. In addition, it was associated with mild clinical and biochemical toxicities, and often these symptoms were relieved over time.

With the increasing incidence of ICC and impossibility of surgical resection, more and more people are exploring new treatments. TARE with ^{90}Y microspheres has gradually become an effective treatment by using an intra-arterial injection of microspheres loaded with ^{90}Y microspheres as the source of internal radiation.[27] Al-A dra et al[9] reported the OS of 15.5 months in the pooled analysis for the treatment of ICC with ^{90}Y radioembolization. However, seven abstracts were included in the pooled analysis, which provided limited information regarding treatment and follow-up outcomes. In the current pooled analysis, we excluded abstracts and added literature published in recent years, which provided more comprehensive information. We came to a similar median OS of 14.3 months. Subgroup analysis was performed based on the type of microspheres, and the median OS was similar in the resin and glass microspheres groups (14.0 vs 14.3 months). Unfortunately, due to the heterogeneity of studies in each group, the random effects model was performed, which failed to compare the differences between groups. Nezami et al[28] compared the dose of

Table 1 Study design and baseline characteristics

Author	Year	Study design	Patient	Mean age	Male, N (%)	ECOG score				Extrahepatic metastases N (%)	Evidence level	Prechemotherapy N (%)	Postchemotherapy N (%)
						0	1	2	3				
Saxena et al[26]	2010	PC	25	57	13 (52.0)	15	7	3	0	12 (48.0)	Moderate	18 (72.0)	7 (28.0)
Mosconi et al[25]	2016	RC	23	65	14 (60.9)	18	5	0	0	2 (8.7)	Low	12 (52.2)	4 (17.4)
Rafi et al[24]	2013	PC	19	63.3	7 (36.8)	1	14	4	0	11 (57.9)	Moderate	19 (100.0)	N/A
Mouli et al[23]	2013	PC	46	68[a]	25 (54.3)	24	21	1	0	16 (34.8)	Moderate	16 (34.8)	N/A
Hoffmann et al[22]	2012	RC	33	65.2	18 (54.5)	17	7	9	0	8 (24.2)	Moderate	27 (78.8)	N/A
Jia et al[21]	2017	RC	24	61.8	8 (33.3)	16	8	0	0	3 (12.5)	Moderate	24 (100.0)	N/A
Soydal et al[20]	2016	RC	16	55.4	8 (50.0)	N/A	N/A	N/A	N/A	5 (31.3)	Moderate	9 (56.3)	N/A
Swinburne et al[19]	2017	RC	29	66	14 (48.3)	11	13	5	0	11 (37.9)	Moderate	15 (51.7)	N/A
Reimer et al[18]	2018	RC	21	69.5	12 (57.1)	0	3	16	2	3 (14.3)	Moderate	0 (0.0)	N/A
Orwat et al[17]	2017	RC	16	N/A	N/A	N/A	N/A	N/A	N/A	N/A	Moderate	N/A	N/A
Paprottka et al[16]	2017	RC	35	N/A	N/A	N/A	N/A	N/A	N/A	N/A	Moderate	N/A	N/A
Gangi et al[13]	2018	RC	85	73.4	41 (48.2)	35	22	28	0	36 (42.4)	Moderate	61 (71.8)	6(7.1)
Filippi et al[11]	2015	PC	17	59.4	6 (35.3)	N/A	N/A	N/A	N/A	4 (23.5)	Moderate	15 (88.2)	N/A
Beuzit et al[12]	2016	RC	45	64[a]	24 (53.3)	25	20		0	N/A	Moderate	41 (91.1)	N/A
Shaker et al[14]	2018	RC	17	69.3	7 (41.2)	N/A	N/A	N/A	N/A	7 (41.2)	Moderate	5 (29.4)	3 (17.6)
Camacho et al[15]	2014	PC	21	62.7[a]	13 (62.0)	9	8	3	0	N/A	Moderate	21 (100.0)	N/A

Note: [a]Median age.

Abbreviations: ECOG, Eastern Cooperative Oncology Group; RC, Retrospective cohort; PC, Prospective cohort; N/A, not available.

Table 2 Treatment characteristics and efficacy

Author	Year	Microsphere	Dosimetric calculation	Follow-up (months)	Median OS (months)	1-year survival	Evaluation criteria	Recist			
								CR	PR	SD	PD
Saxena et al[26]	2010	Resin	BSA	8.1	9.3	40.0%	RECIST	0	6	11	5
Mosconi et al[25]	2016	Resin	BSA	16.0	17.9	67.9%	RECIST	0	4	11	5
							mRECIST	1	13	3	3
							EASL	1	11	5	3
Rafi et al[24]	2013	Resin	BSA	15.0	11.5	56.0%	RECIST	0	2	13	4
Mouli et al[23]	2013	Glass	N/A	29.0	N/A	N/A	WHO	0	11	33	1
							EASL	4	28	-	0
Hoffmann et al[22]	2012	Resin	BSA	10	22.0	N/A	RECIST	0	12	17	5
Jia et al[21]	2017	Resin	BSA	11.3[d]	9.0	32.6%	mRECIST	-	8	10	4
Soydal et al[20]	2016	Resin	BSA	8.1	9.7	N/A	RECIST	-	-	-	-
Swinburne et al[19]	2017	Resin/glass	BSA; Other[a]	8.4[d]	9.1	N/A	RECIST	0	3	16	7
Reimer et al[18]	2018	Resin	BSA	N/A	15.0	N/A	RECIST	0	1	9	11
Orwat et al[17]	2017	Resin/glass	BSA	N/A	5.2	N/A	N/A	N/A	N/A	N/A	N/A
Paprottka et al[16]	2017	Resin	mBSA	N/A	14.3	N/A	RECIST	N/A	N/A	N/A	N/A
Gangi et al[13]	2018	Glass	Other[b]	9.8	12.0	49.0%	RECIST	0	5	52	24
Filippi et al[11]	2015	Resin	BSA	N/A	17.0	N/A	PERCIST	0	14	3	0
Beuzit et al[12]	2016	Glass	N/A	N/A	19.0	54.0%	RECIST	0	6	32	7
							Choi	-	37	2	6
Shaker et al[14]	2018	Resin/glass	N/A	21.3[d]	33.6	N/A	N/A	N/A	N/A	N/A	N/A
Camacho et al[15]	2014	Resin	BSA; other[c]	N/A	16.3	N/A	RECIST	0	1	13	2
							mRECIST	2	7	5	2
							EASL	2	6	6	2

Notes: [a]TheraSphere dosimetry was calculated based upon a desired radiation treatment dose for a targeted portion of the liver. [b]Dosimetry was calculated based on the treated liver volume, the administered activity, and the lung shunt fraction. [c]Dosimetry was based on tumor volumetry and then adjusted by the pulmonary shunt fraction. [d]Mean follow-up.

Abbreviations: RECIST, Response Evaluation Criteria in Solid Tumors; PERCIST, Positron Emission Tomography Response Criteria in Solid Tumors; mRECIST, modified RECIST; EASL, the European Association for the Study of the Liver; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; OS, overall survival; N/A, not available; BSA, body surface area.

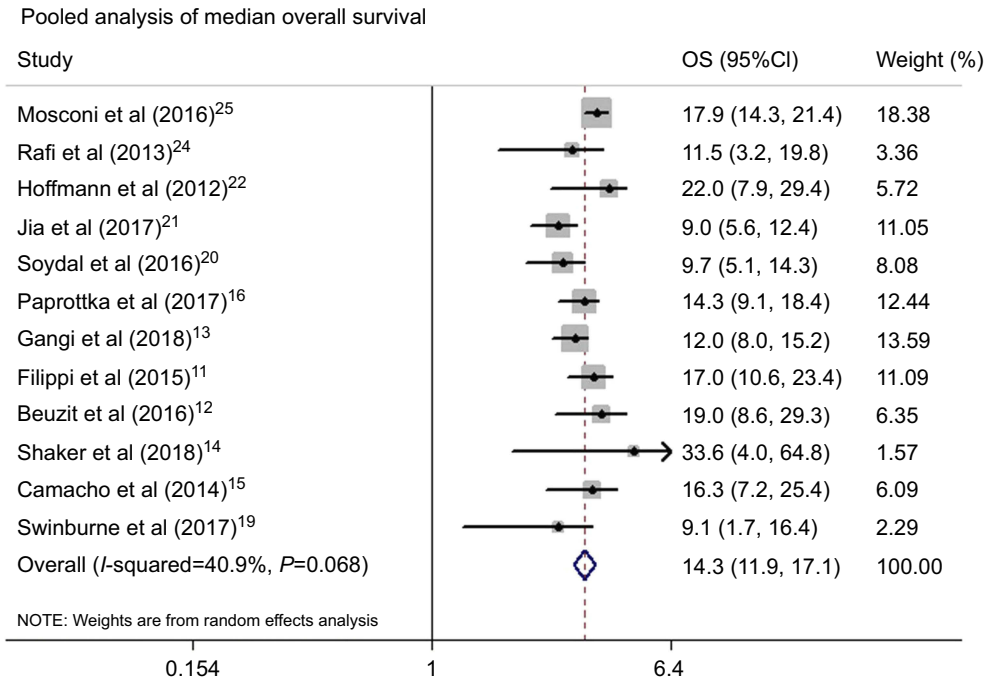

Figure 2 Pooled analysis of median overall survival.
Abbreviation: OS, overall survival.

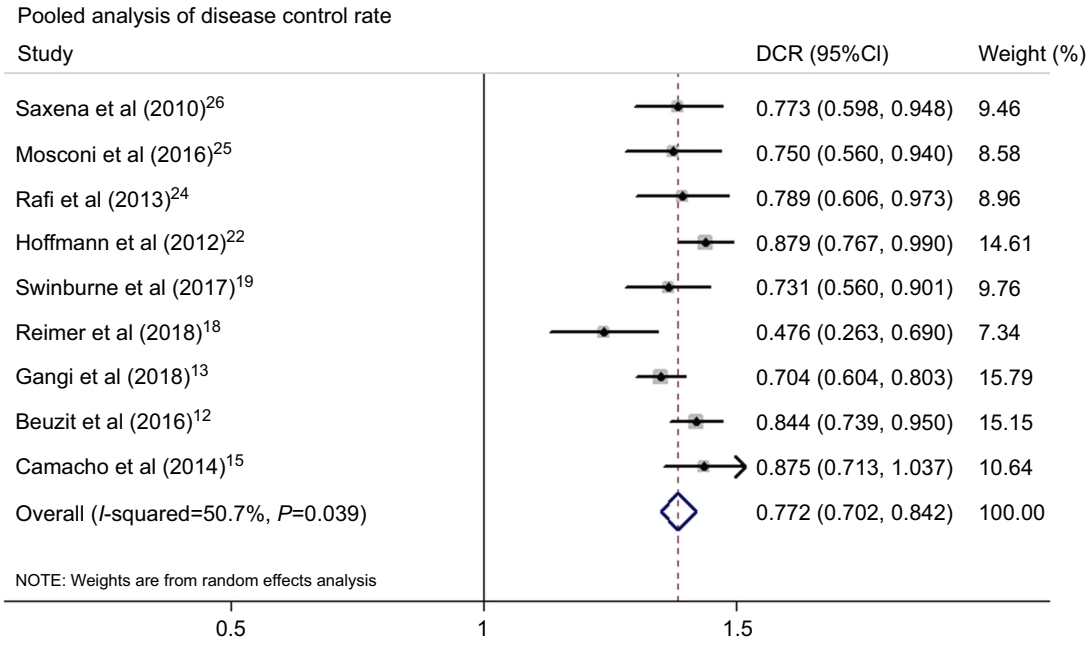

Figure 3 Pooled analysis of disease control rate.
Abbreviation: DCR, disease control rate.

radiation delivered through glass and resin-based ^{90}Y microspheres to ICC and concluded that ^{90}Y both glass and resin-based microspheres radioembolization were feasible and safe in the treatment of ICC, while glass microsphere delivers a higher dose of ^{90}Y to the targeted tumors. However, it remains to be further studied whether the two types of microspheres affect the prognosis of ICC patients. Ray et al[29] reported that the pooled median OS of transarterial chemoembolization (TACE) for unresectable ICC was 13.4 months. Boehm et al[30]

Table 3 Clinical and biochemical toxicities

Author	Year	Clinical toxicities, N (%)							Biochemical Toxicities, N (%)			Severity, N (%)
		Fatigue	Anorexia	Abdominal pain	Nausea	Vomiting	Ascites	Gastroduodenal ulceration	Abumin	Bilirubin	Alkaline phosphatase	Grade III–IV[a]
Saxena et al[26]	2010	16 (64.0)	4 (16.0)	10 (40.0)	4 (16.0)	2 (8.0)	4 (16.0)	1 (4.0)	1 (4.0)	1 (4.0)	1 (4.0)	4 (16.0)
Mosconi et al[25]	2016	2 (8.7)	N/A	5 (21.7)	N/A	N/A	5 (21.7)	N/A	N/A	1 (4.3)	N/A	2 (8.6)
Rafi et al[24]	2013	4 (21.0)	N/A	6 (32.0)	N/A	N/A	N/A	0	N/A	3 (15.8)	N/A	2 (11.0)
Mouli et al[23]	2013	25 (54.0)	2 (4.0)	13 (28.0)	6 (13.0)	4 (9.0)	7 (15.0)	1 (2.0)	4 (9.0)	3 (7.0)	0	8 (18.0)
Hoffmann et al[22]	2012	N/A	N/A	28 (85.0)	20 (61.0)	9 (27.0)	N/A	N/A	N/A	23 (70.0)	N/A	N/A
Jia et al[21]	2017	21 (87.5)	19 (79.2)	10 (58.3)	15 (62.5)	4 (16.7)	N/A	1 (4.2)	0	0	0	6 (25.0)
Soydal et al[20]	2016	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Swinburne et al[19]	2017	2 (6.7)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	4 (13.3)	1 (3.3)	0
Reimer et al[18]	2018	0	0	0	0	0	0	1 (5.0)	0	0	0	1 (5.0)
Orwat et al[17]	2017	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Paprottka et al[16]	2017	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Gangi et al[13]	2018	36 (42.3)	N/A	16 (18.8)	N/A	N/A	5 (5.9)	N/A	N/A	N/A	39 (46.0)	6 (7.0)
Filippi et al[11]	2015	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	1 (4.0)
Beuzit et al[12]	2016	N/A	N/A	N/A	N/A	N/A	1 (2.0)	N/A	N/A	N/A	N/A	1 (2.0)
Shaker et al[14]	2018	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Camacho et al[15]	2014	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Note: [a]Grade III–IV toxicities including gastroduodenal ulceration.
Abbreviation: N/A, not available.

conducted a pooled median OS of 12.4 months for the treatment of TACE. It seems that median OS of TARE with ^{90}Y microspheres was generally consistent with TACE. However, further randomized controlled trials are needed to confirm these results.

In the current pooled analysis, most of the studies (11/16) evaluated tumor response according to RECIST, and the pooled DCR was 77.2%, which indicated that TARE was an effective treatment for ICC. However TARE with ^{90}Y microspheres usually leads to necrosis without an actual decrease of tumor size, RECIST[31,32] only considers the change in the size of target lesions, and the association between RECIST and survival still needs further to be investigated. PET can evaluate the change of tumor volume through the difference of standardized uptake value, which is valuable in assessing the activity of cancer therapies that stabilize diseases.[33] Zerizer et al[34] reported that 18F-FDG PET-CT was superior to RECIST in evaluating early response of TARE and predicting progression free survival in patients with liver metastases. Therefore, PET-based approaches are expected to be effective evaluation criteria in tumor response after TARE with ^{90}Y microspheres.

In addition, TARE with ^{90}Y microspheres is associated with some side effects. In the current pooled analysis, the common clinical toxicities mainly included fatigue, abdominal pain, nausea, vomiting, ascites, and biochemical toxicities had decreased albumin, elevated bilirubin and alkaline phosphatase, etc. These side effects were usually mild and acceptable, and could be resolved without medical therapy. Moreover, gastroduodenal ulceration is a relatively common serious side effect of TARE with ^{90}Y microspheres,[35] which is caused by nontargeted microsphere distribution, so it is necessary to clarify the vascular anatomy and undergo prophylactic arterial embolization; in addition, microspheres must be carefully injected during the treatment process to avoid nontargeted embolization.

There are several limitations in the current pooled analysis. First, in the pooled analysis, not all studies reported the population and treatment characteristics that were meta-analyzed, thus not allowing a complete analysis of heterogeneity sources. Second, meta-regression was not performed in the current analysis because the pooled results were robust in the sensitivity analysis, which suggested the source of heterogeneity may not exist in studies, but in individuals. Third, side effects were summarized only as descriptive words, standardized methodology needs to be used. Fourth, the current results failed to help define the best population for TARE, but this pooled analysis included the best available evidence and provided valuable information on the therapeutic efficacy and safety of TARE with ^{90}Y microspheres for unresectable ICC.

Conclusion

TARE with ^{90}Y microspheres is a promising therapeutic option for patients with unresectable ICC with acceptable side effects. The different microspheres seem to have no influence on therapeutic efficacy, and TARE with ^{90}Y microspheres has a similar OS compared with TACE reported in previous studies. A large sample of randomized controlled trial is warranted to confirm the above results.

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Author contributions

All authors contributed to data analysis, drafting and revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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