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Comparison of Radioembolization and Sorafenib for the Treatment of Hepatocellular Carcinoma with Portal Vein Tumor Thrombosis: A Systematic Review and Meta-Analysis of Safety and Efficacy

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Objective: To compare the safety and efficacy of radioembolization with that of sorafenib for the treatment of hepatocellular carcinoma (HCC) with portal vein tumor thrombosis (PVTT).

Materials and Methods: MEDLINE, EMBASE, and Cochrane databases were searched for studies reporting outcomes in patients with HCC and PVTT treated with radioembolization or sorafenib. Meta-analyses of cumulative overall survival (OS) and Kaplan-Meier survival rates according to the time to progression (TTP) and incidence of adverse events (AEs) were performed. Subgroup analyses were conducted on 1-year OS data.

Results: Seventeen studies were identified (four involving radioembolization, 10 involving sorafenib, and three comparing both). Pooled OS rates were higher in the radioembolization group, notably at 6 months {76% (95% confidence interval [CI], 64–85%) vs. 54% (95% CI, 45–62%)} and 1 year (47% [95% CI, 38–57%] vs. 24% [95% CI, 18–30%]); TTP was also longer with radioembolization. In patients undergoing radioembolization, the proportion of patients with Eastern Cooperative Oncology Group status 0 ($p < 0.0001$), Child-Pugh A ($p < 0.0001$), extrahepatic metastasis ($p = 0.0012$), and a history of cancer treatment ($p = 0.0048$) was identified as a significant source of heterogeneity for the 1-year OS. Radioembolization was associated with a lower incidence of grade 3/4 AEs than sorafenib (9% [95% CI, 3–27%] vs. 28% [95% CI, 17–43%]).

Conclusion: Compared with sorafenib, radioembolization is a safer and more effective treatment for HCC with PVTT and is associated with prolonged survival, delayed tumor progression, and fewer grade 3/4 AEs.

Keywords: *Hepatocellular carcinoma; Portal vein tumor thrombosis; Radioembolization; Sorafenib; Meta-analysis*

INTRODUCTION

Primary liver cancer is the fourth most common cause of cancer-related death worldwide (1), with hepatocellular carcinoma (HCC) accounting for 90% of primary liver cancers (2). Portal vein tumor thrombosis (PVTT) is a major concern in patients with HCC, developing in > 30% of patients during the disease course and presenting as an initial manifestation in 10–40% of the patients (3). PVTT is a strong negative prognostic factor and is associated with a median survival of only 2–4 months if left untreated (3-5). Therefore, the Barcelona Clinic Liver Cancer (BCLC) guidelines classify HCC with PVTT as advanced-stage disease (BCLC stage C) (2).

Sorafenib is currently the only evidence-based therapeutic option for patients with HCC and PVTT, and is recommended by the BCLC, American Association for the Study of Liver Diseases, and European guidelines (2, 6, 7). However, studies of sorafenib for the treatment of HCC with PVTT have

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shown a median overall survival (OS) period of only 3.1–6.0 months (8-11). Sorafenib therapy is also associated with poor tolerability and discontinuation, and dose reduction is often required due to adverse events (AEs) such as diarrhea, fatigue, and hand-foot skin reaction (12-15). Therefore, ongoing research aims to identify alternative treatments that may improve OS and maintain good compliance.

Radioembolization with yttrium-90 (^{90}Y), also referred to as selective internal radiation therapy, is a promising therapeutic option for primary and metastatic liver cancer (16, 17). ^{90}Y-loaded microspheres are delivered to the blood vessels supplying the tumor via the hepatic artery, allowing localized high-dose radiation to be delivered to the hepatic tumors. The small microspheres deliver radiation with a short depth of penetration (approximately 2.5 mm), thereby effectively inducing tumor necrosis while sparing the surrounding normal liver parenchyma. There is growing evidence to support the use of radioembolization, particularly in the treatment of HCC with PVTT (18-21). Three retrospective studies have compared treatment with radioembolization and sorafenib in this patient group (22-24), and two of these demonstrated favorable OS with radioembolization (22, 23). In addition, severe AEs were less frequent in patients undergoing radioembolization (3–18% vs. 16–45% in the sorafenib groups) (22, 24).

However, the lack of large prospective studies or randomized controlled trials means that there is currently insufficient evidence to support the widespread use of radioembolization for the treatment of HCC with PVTT. We therefore performed a systematic review and meta-analysis of available studies to evaluate and compare the safety and efficacy of radioembolization and sorafenib for the treatment of patients with HCC and PVTT.

MATERIALS AND METHODS

This study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (25).

Search Strategy and Eligibility Criteria

A search of the MEDLINE/PubMed, EMBASE, and Cochrane databases was conducted to identify original studies of the safety and efficacy of radioembolization or sorafenib for the treatment of HCC with PVTT, using pertinent MESH terms and common keywords (Supplementary Table 1 in the online-only Data Supplement). All publications until 14 September 2018 were included in this initial search. Bibliographies of relevant articles were also searched as well as Google and Google Scholar. The search was restricted to English language articles.

After eliminating duplicates, articles were screened on the basis of the title and abstract; case reports, reviews, letters, and conference abstracts were excluded. Full-text articles were then thoroughly assessed according to the following eligibility criteria: 1) population: patients diagnosed with HCC with PVTT; 2) intervention/exposure: treatment with radioembolization and follow-up after treatment; 3) comparison: treatment with sorafenib and follow-up after treatment; 4) outcome: cumulative OS rates or sufficient details to enable indirect estimation of OS rates. Publications were excluded if they met any of the following criteria: 1) articles investigating issues not directly relevant to this study; 2) studies that included patients with and without PVTT where data from the two groups could not be separated; 3) studies that included patients who had previously undergone counterpart therapy (radioembolization or sorafenib), where data could not be separated; 4) insufficient data to obtain cumulative survival rates; 5) sample size < 20 patients; 6) data included in subsequent articles or duplicate reports.

The literature search and application of criteria were conducted independently by two authors; any discrepancy was resolved through discussion and consensus with a third author.

Data Extraction and Study Endpoints

The following variables were extracted from the eligible studies: 1) study characteristics (first author, publication year, study design, study location, and period); 2) demographic and patient characteristics (sample size, patient age and sex, etiology of HCC, Eastern Cooperative Oncology Group [ECOG] performance status, Child-Pugh class, history of previous treatment); 3) tumor characteristics (alpha-fetoprotein [aFP] level, tumor size, tumor burden, main portal vein involvement, extrahepatic metastasis); and 4) types of intra-arterial vectors used for radioembolization (glass or resin-based). Data extraction was independently conducted by the two authors, and any discrepancy was arbitrated by a third. Any additional patient data were requested from the study authors when necessary.

The primary study outcome was OS at 3 and 6 months, and 1, 2, and 3 years. The secondary study outcomes

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were the Kaplan-Meier (KM) rates according to time to progression (TTP) analysis and AEs. Engauge Digitizer (Version 10.7; http://markummitchell.github.io/engauge-digitizer) was used to extract survival rates from KM curves when necessary. AEs were defined and categorized in accordance with National Cancer Institute-Common Terminology Criteria for Adverse Events version 5.0.

Quality Assessment

The quality of the eligible studies was independently evaluated using the US National Institutes of Health Quality Assessment of Case Series Studies tool (26). Two reviewers independently evaluated the quality, with all discrepancies being resolved at a consensus meeting in the presence of a third reviewer.

Data Synthesis and Statistical Analysis

Meta-analyses were based on the inverse variance method for calculating weights. Pooled OS, KM rates according to TTP analysis, and incidence rates of AEs (including 95% confidence intervals [CIs]) were determined using the restricted maximum-likelihood estimation of the random-effects model. Heterogeneity across studies was evaluated using the Cochrane Q-test and the I^2 statistic. A p value < 0.10 in the Q-test was considered to indicate substantial heterogeneity. I^2 was interpreted as suggested in the literature: 0–25%, might not be important; 25–50%, low heterogeneity; 50–75%, moderate heterogeneity; and 75–100%, high heterogeneity (27). Publication bias was evaluated using the funnel plot and Egger's test, with $p < 0.1$ indicating significant publication bias (28).

Meta-regression analyses were performed to examine the source of heterogeneity for the 1-year OS rate, stratified by treatment arms. All statistical analyses were performed using R software (version 3.1.2; R Foundation for Statistical Computing, Vienna, Austria) with the "metafor" package, and line graphs were drawn with the "ggplot2" package.

RESULTS

Literature Selection

A total of 288 non-duplicated studies were identified,

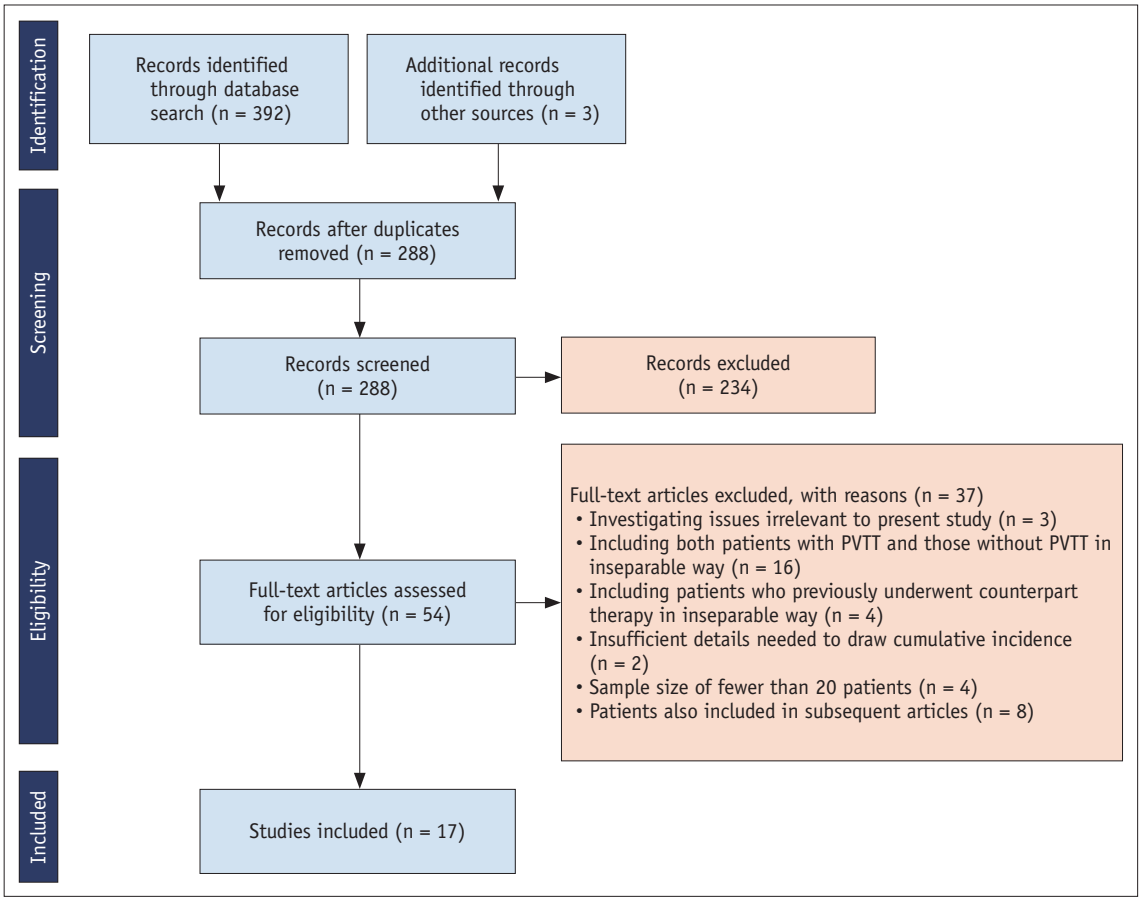

Fig. 1. Flowchart of publication selection process. PVTT = portal vein tumor thrombosis

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285 from the databases, and 3 from the Google search (Fig. 1). Of these, 234 articles were excluded on the basis of their titles and abstract and 54 potentially eligible full-text articles were assessed according to the eligibility criteria. Seventeen studies met the eligibility criteria and were included in the analysis (8-11, 13, 19-24, 29-34).

Study Characteristics

The detailed study characteristics are summarized in Table 1. Four studies reported radioembolization data (19-21, 33), ten reported sorafenib data (8-11, 13, 29-32, 34), and three compared both treatments using a retrospective approach (22-24). Among the studies investigating radioembolization, four used glass-based intra-arterial vectors (19, 20, 22, 33), two used resin-based vectors (23, 24), and one used both (21). Six studies were prospective (13, 19, 29, 32-34), and eleven were retrospective (8-11, 20-24, 30, 31). Sample size ranged from 22 to 269 patients, and the mean patient age ranged from 48 years to 72 years. The proportion of patients with ECOG 0 was 0–96%; Child-Pugh class A, 47–100%; aFP ≥ 400 ng/mL, 35–67%; tumor burden ≥ 50% of the liver, 0–55%; extrahepatic metastasis, 0–63%; main portal vein involvement, 0–100%; and no history of previous cancer treatment, 50–100%. The mean/median maximum tumor size was 6.0–11.2 cm.

Previous cancer treatments included transcatheter arterial chemoembolization (TACE) or transcatheter arterial chemotherapy infusion, radiofrequency ablation, external beam radiotherapy, or liver transplantation.

Study Quality

The quality of the studies included in this analysis was assessed to be good (n = 14) or fair (n = 3). Therefore, no publications were excluded from the analysis on the basis of quality. Further details of study quality are shown in Supplementary Table 2 in the online-only Data Supplement.

OS: Meta-Analysis

Seven studies were analyzed for the pooled OS analysis of patients treated with radioembolization (19-24, 33). The meta-analysis showed that the 3-month, 6-month, and 1-, 2-, and 3-year OS rates were 93% (95% CI, 86–98%; I^2 = 82.4%), 76% (95% CI, 64–85%; I^2 = 83.7%), 47% (95% CI, 38–57%; I^2 = 70.3%), 27% (95% CI, 17–38%; I^2 = 82.5%), and 16% (95% CI, 7–27%; I^2 = 84.8%), respectively (Fig. 2). Moderate to high study heterogeneity was observed at

Table 1. Study Characteristics

First Author (Year)	Country	Study Design	Study Period	Treatment	No. of Patients	Mean/Median Age (Range)	Male/ Female	Etiology (HBV/HCV/ Alcohol/Others)
Tsai (2010) (21)	USA	Retrospective	-	RE (G, R)	22	58 (18–78)	20/2	-
Jeong (2013) (8)	Korea	Retrospective	2008–2011	SOR	30	58 (41–84)	21/9	24/2/3/1
Mazzaferro (2013) (19)	Italy	Prospective	2007–2009	RE (G)	35	64 (32–82)	34/1	12/11/-/-
Nakazawa (2014) (31)	Japan	Retrospective	2009–2011	SOR	36	70 (62–78)	31/5	-/19/-/-
Kim (2015) (9)	Korea	Retrospective	1997–2012	SOR	66	52 (46–59)‡	54/12	57/3/-/-
Song (2015) (10)	Korea	Retrospective	2008–2013	SOR	60	56 (9.0)§	44/16	41/5/8/6
Zhang (2015) (11)	China	Retrospective	2009–2013	SOR	44	54 (9.7)§	41/3	42/-/-/-
Cho (2016) (24)	Korea	Retrospective	2008–2013	RE (R)	32	64 (11.1)§	26/6	23/5/2/3
				SOR	31	60 (10.4)§	30/1	30/0/1/0
de la Torre (2016) (23)	Spain	Retrospective	2005–2013	RE (R)	26	66 (57–69)‡	23/3	-
				SOR	47	63 (52–70)‡	39/8	-
Edeline (2016) (22)	France	Retrospective	2005–2012	RE (G)	34	64 (8.9)§	27/7	-/-/11/13
				SOR	117	65 (10.4)§	106/11	-/-/36/49
Giorgio (2016) (29)	Italy	Prospective†	2011–2014	SOR	50	72 (70–76)	36/14	17/27/-/-
Kuo (2018) (30)	China	Retrospective	2012–2015	SOR	113	65 (38–90)	91/22	51/44/-/-
Ye (2017) (32)	China	Prospective	2009–2012	SOR	115	48 (11.9)§	108/7	102/-/-/-
Ali (2018) (33)	USA	Prospective	2003–2017	RE (G)	269	-	410/137*	-
Choi (2018) (34)	Korea	Prospective†	2013-2016	SOR	29	60 (7.3)§	27/2	18/5/6/0
Spreafico (2018) (20)	Italy	Retrospective	2010–2015	RE (G)	120	64 (56–72)‡	102/18	34/61/18/13
Yoon (2018) (13)	Korea	Prospective†	2013–2016	SOR	45	55 (33–82)	39/6	40/0/-/-

*Data only available for entire study population only, †Randomized controlled trial, ‡Interquartile range, §Standard deviation. G = glass, HBV = hepatitis B virus, HCV = hepatitis C virus, R = resin, RCT= randomized controlled trial, RE = radioembolization, SOR = sorafenib

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Table 1. Study Characteristics (continued)

First Author (Year)	Treatment	ECOG 0/1/2/3	Child-Pugh Class (A/B/C)	aFP ≥ 400 ng/mL	Mean/Median Maximum Tumor Size, cm	Tumor Burden ≥ 50%	MPV Involvement	Extra-Hepatic Metastasis	Previous Treatment	
									No.	Yes (TACE or TACI/RFA/ Resection/ Other†)
Tsai (2010) (21)	RE (G, R)	-	12/6/1‡	-	-	4 (18)	-	3 (14)	-	-
Jeong (2013) (8)	SOR	0/20/10/0	17/13/0	19 (63)	-	-	24 (80)	19 (63)	15 (50)	17/0/0/5
Mazzaferro (2013) (19)	RE (G)	14/21/0/0	28/7/0	-	6.6	0 (0)	6 (17)	0 (0)	27 (77)	0/5/3/0
Nakazawa (2014) (31)	SOR	-	36/0/0	-	-	-	7 (19)	7 (19)	10 (28)	21/3/0/2
Kim (2015) (9)	SOR	-/-/7/0	43/23/0	43 (65)	-	-	-	33 (50)	66 (100)	0/0/0/0
Song (2015) (10)	SOR	-	47/13/0	-	-	-	39 (65)	21 (35)	39 (65)	-
Zhang (2015) (11)	SOR	0/39/5/0	34/10/0	-	-	24 (55)	44 (100)	-	44 (100)	0/0/0/0
Cho (2016) (24)	RE (R)	-	28/4/0	-	-	7 (23)§	0 (0)	0 (0)	22 (69)	-
	SOR	-	22/9/0	-	-	8 (26)	15 (48)	0 (0)	27 (87)	-
de la Torre (2016) (23)	RE (R)	-	-	-	11.2	-	-	4 (15)	-	-
	SOR	-	-	-	6.0	-	-	15 (32)	-	-
Edeline (2016) (22)	RE (G)	29/-/-/-	31/3/0	12 (35)	7.5	5 (15)	16 (47)	0 (0)	-	-
	SOR	67/-/-/-	92/25/0	56 (48)	7.9	13 (11)	55 (47)	0 (0)	-	-
Giorgio (2016) (29)	SOR	-	50/0/0	-	4.3	-	50 (100)	0 (0)	50 (100)	0/0/0/0
Kuo (2018) (30)	SOR	0/0/113/0	113/0/0	43 (38)	7.9	-	-	-	-	-
Ye (2017) (32)	SOR	30/69/-/-	80/-/-	77 (67)	8.2	54 (47)	-	42 (37)	40 (35)	54/4/-/-
Ali (2018) (33)	RE (G)	130/380/ 37/0*	259/288/0*	-	-	-	-	89 (16)*	499 (91)*	26/0/8/14*
Choi (2018) (34)	SOR	-/-/0/0	25/4/0	-	-	-	18 (62)	0 (0)	26 (90)	-
Spreafico (2018) (20)	RE (G)	115/5/0/0	112/8/0	-	7.4	24 (20)	0 (0)	0 (0)	-	-
Yoon (2018) (13)	SOR	22/23/0/0	45/0/0	-	9.6	-	27 (60)	0 (0)	45 (100)	0/0/0/0

Data are shown as n (%). *Data available for entire study population only, †Including radiotherapy and liver transplantation, ‡Information was not available in three patients, §Information was not available in one patient. aFP = alpha-fetoprotein, ECOG = Eastern Cooperative Oncology Group, MPV = main portal vein, RFA = radiofrequency ablation, TACE = transcatheter arterial chemoembolization, TACI = transcatheter arterial chemotherapy infusion

all points. No significant publication bias was detected with the exception of the 3-year OS (p = 0.062) (Supplementary Fig. 1 in the online-only Data Supplement).

Thirteen studies were analyzed for the pooled OS analysis of patients treated with sorafenib (8-11, 13, 22-24, 29-32, 34). The meta-analysis yielded 3-month, 6-month, and 1-, 2-, and 3-year OS rates of 82% (95% CI, 76–87%; I^2 = 74.5%), 54% (95% CI, 45–62%; I^2 = 82.5%), 24% (95% CI, 18–30%; I^2 = 71.3%), 11% (95% CI, 7–17%; I^2 = 67.4%), and 7% (95% CI, 2–13%; I^2 = 75.1%), respectively (Fig. 2). Although no significant publication bias was detected (Supplementary Fig. 1 in the online-only Data Supplement), moderate to high study heterogeneity was observed at all points.

Comparison of the two treatment arms showed that OS was higher in patients undergoing radioembolization than in those treated with sorafenib at all points, with this difference being significant at the 6-month and 1-year timepoints (Fig. 3).

TTP: Meta-Analysis

Two studies were included in the pooled analysis of KM rates according to TTP in patients treated with radioembolization (19, 24). Meta-analysis showed that the 3-month, 6-month, and 1- and 2-year KM survival rates were 32% (95% CI, 15–51%; I^2 = 60.2%), 46% (95% CI, 34–58%; I^2 = 0%), 63% (95% CI, 49–77%; I^2 = 27.7%), and 63% (95% CI, 49–77%; I^2 = 27.7%), respectively (Fig. 4).

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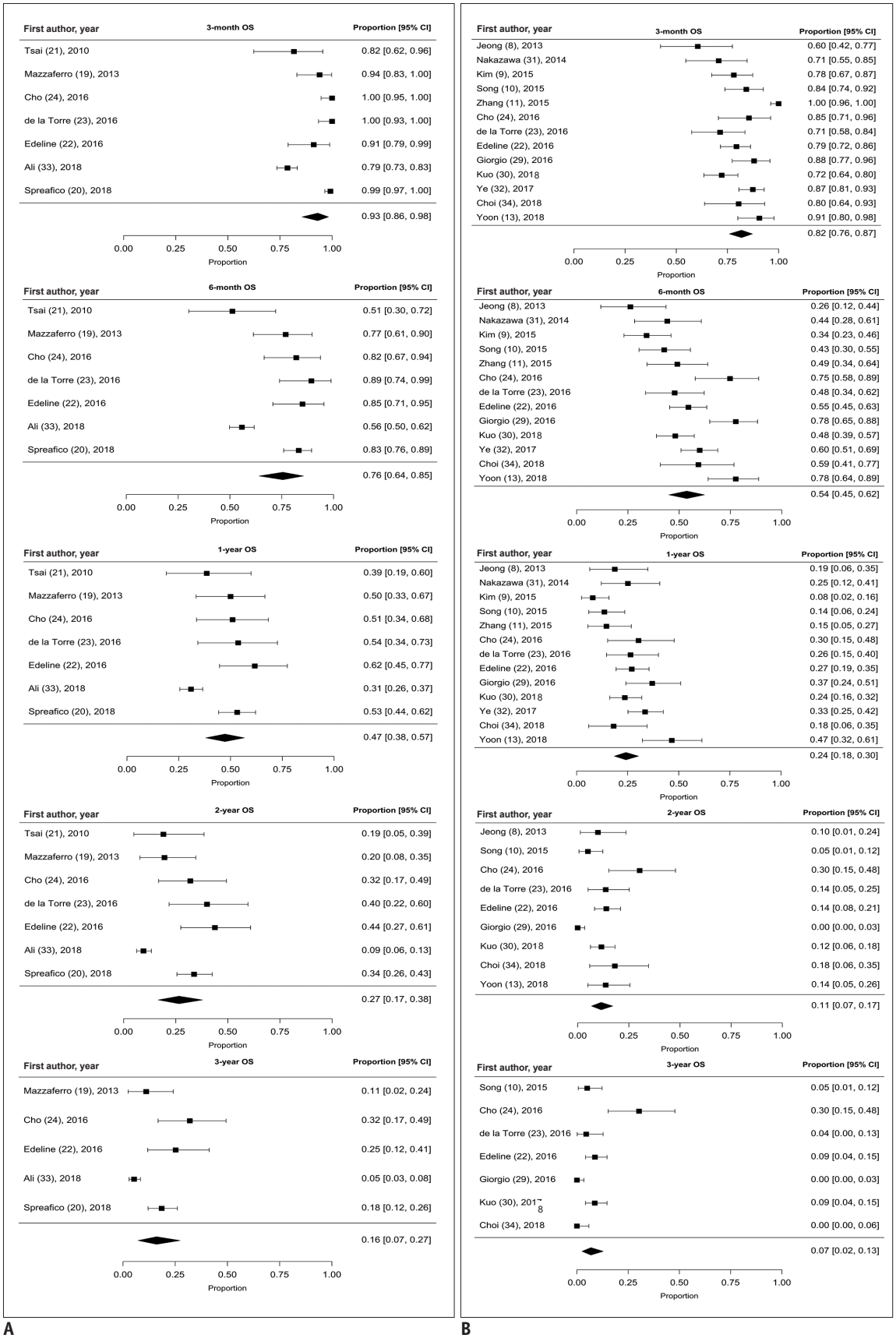

Fig. 2. Forest plots of OS for (A) RE and (B) SOR. CI = confidence interval, OS = overall survival, RE = radioembolization, SOR = sorafenib

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Pooling of the 3-year data was not possible because data were available from only a single study at that timepoint (24). No substantial study heterogeneity was observed, with the exception of the 3-month timepoint. No significant publication bias was detected (Supplementary Fig. 2 in the online-only Data Supplement).

Six studies were included in the analysis of pooled KM rates according to TTP in patients treated with sorafenib (9-11, 24, 30, 34). Meta-analysis showed that the 3-month, 6-month, and 1-, 2-, and 3-year KM survival rates were 62% (95% CI, 55–69%; I^2 = 39.4%), 87% (95% CI, 76–95%; I^2 = 84.1%), 94% (95% CI, 84–99%; I^2 = 78.2%), 93% (95% CI, 77–100%; I^2 = 82.8%), and 93% (95% CI, 77–100%; I^2 = 82.8%), respectively (Fig. 4). While no significant publication bias was detected (Supplementary Fig. 2 in the online-only Data Supplement), moderate to high study heterogeneity was observed at all except the 3-month timepoint.

When comparing the two treatment arms, the KM rate was lower in the radioembolization versus the sorafenib group at all timepoints, with significant differences seen at the 3-month, 6-month, and 1-year timepoints (Fig. 3).

Meta-Regression Analysis for 1-Year OS

Meta-regression analysis including whole studies regardless of treatment arms revealed that the 1-year OS rate was significantly higher in the radioembolization group, compared with the sorafenib group (p < 0.0001).

Among patients undergoing radioembolization, the proportions of patients in the study population with ECOG 0 (p < 0.0001), Child-Pugh A (p < 0.0001), extrahepatic metastasis (p = 0.0012), and a previous history of HCC treatment (p = 0.0048) were identified as a significant source of heterogeneity. Indeed, there was a 0.33%, 0.53%, and 1.04% increase in the 1-year OS for every 1% increase in the proportion of patients with ECOG 1, Child-Pugh A, and a previous history of HCC treatment, and a 1.12% decrease in the 1-year OS was seen for every 1% increase in the proportion of patients with extrahepatic metastasis.

In patients receiving sorafenib, publication year (p = 0.0127) was identified as significant sources of heterogeneity. Indeed, there was a 4.43% increase in 1-year OS for every 1-year increase in the publication year. Detailed results of the meta-regression analyses are shown in Table 2.

AEs

The pooled incidence of grade 3/4 AEs in patients undergoing radioembolization was 9% (95% CI, 3–27%; I^2 = 37.1%) (Table 3). The pooled estimate showed low study heterogeneity with no significant publication bias (p > 0.999). Pooling of grade 1/2 AEs was not possible because data were only available from a single study (24).

The pooled incidence of grade 1/2 and grade 3/4 AEs in patients receiving sorafenib was 49% (95% CI, 34–64%; I^2 = 83.9%) and 28% (95% CI, 17–43%; I^2 = 88.7%), respectively (Table 4). While publication bias was not observed in either estimate (p = 1.000 and 0.180,

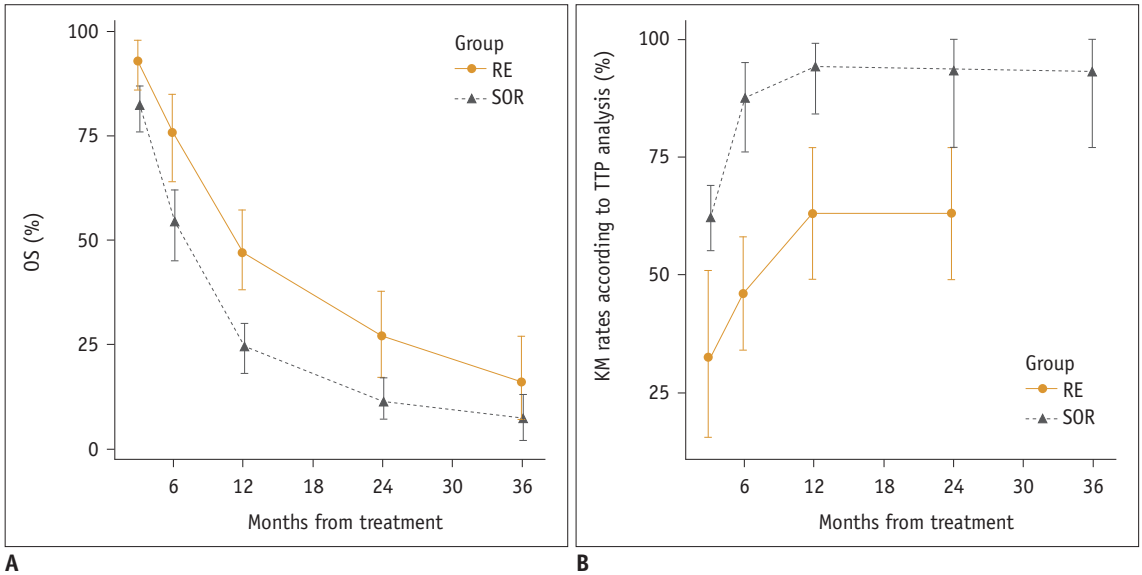

Fig. 3. Meta-analysis estimates of (A) OS and (B) KM rates according to TTP analysis across follow-up period. Error bars represent 95% CI. KM = Kaplan-Meier, TTP = time to progression

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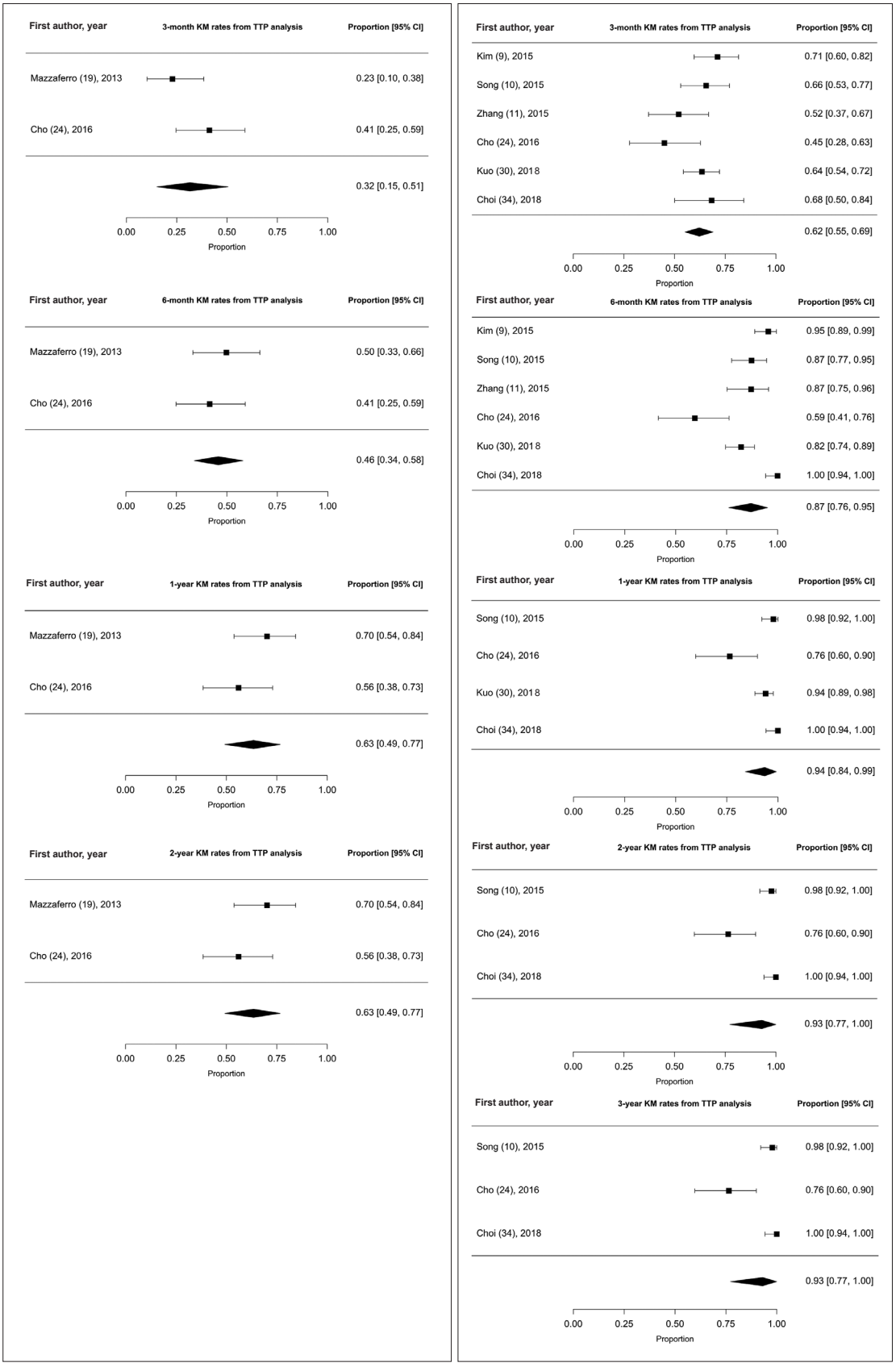

A B

Fig. 4. Forest plots of KM rates according to TTP analysis for (A) RE and (B) SOR.

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Table 2. Summary of Meta-Regression Analyses of 1-Year Overall Survival Data

Study Characteristics	RE		SOR	
	Regression Coefficient (95% CI)	*P*	Regression Coefficient (95% CI)	*P*
Publication year	-0.0010 (-0.0346–0.0326)	0.9545	0.0443 (0.0095–0.0792)	0.0127
Types of vectors				
Glass-based	RD	RD	-	-
Resin-based	0.0682 (-0.1163–0.2527)	0.4688	-	-
Combined	-0.0995 (-0.3810–0.1820)	0.4884	-	-
ECOG 0, %	0.0033 (0.0019–0.0047)	< 0.0001	0.0023 (-0.0001–0.0047)	0.0601
Child-Pugh A, %	0.0053 (0.0032–0.0073)	< 0.0001	0.0034 (-0.0004–0.0072)	0.0776
aFP ≥ 400 ng/mL, %	-	-	-0.0009 (-0.0073–0.0056)	0.7938
Mean/median maximum tumor size, cm	0.0034 (-0.0372–0.0440)	0.8707	0.0058 (-0.0321–0.0437)	0.7629
Intrahepatic tumor burden ≥ 50%, %	0.0004 (-0.0083–0.0091)	0.9291	-0.0003 (-0.0036–0.0029)	0.8470
MPV involvement, %	0.0017 (-0.0022–0.0055)	0.3954	-0.0004 (-0.0032–0.0024)	0.7810
Extrahepatic metastasis, %	-0.0112 (-0.0180–-0.0044)	0.0012	-0.0022 (-0.0047–0.0003)	0.0896
History of previous HCC treatment, %	0.0104 (0.0032–0.0176)	0.0048	0.0001 (-0.0026–0.0028)	0.9175

Study characteristics with percentage as unit indicate proportion of study population. CI = confidence interval, HCC = hepatocellular carcinoma, RD = reference data

Table 3. Summary of Adverse Events Following RE

First Author (Year)	No. of Patients	Grade 1/2 Toxicity Incidence (%)	Grade 1/2 Toxicity	Grade 3/4 Toxicity Incidence (%)	Grade 3/4 Toxicity
Tsai (2010) (21)	22	-	Abdominal pain (n = 12), nausea (n = 9), fatigue (n = 7), anorexia (n = 6), edema (n = 4), vomiting (n = 4), ascites (n = 3), diarrhea (n = 2), constipation (n = 1), dyspnea (n = 1), fever (n = 1), GERD (n = 1), weakness (n = 1), weight loss (n = 1)	-	Ascites (n = 4), encephalopathy (n = 4), fatigue (n = 3), abdominal pain (n = 3), edema (n = 1), weakness (n = 1)
Mazzaferro (2013) (19)	35	-	-	-	Clinical toxicities Anorexia (n = 5), bile duct stenosis (n = 3), nausea/vomiting (n = 3), fatigue (n = 3), abdominal pain (n = 2), ascites (n = 2), variceal hemorrhage (n = 2), cholecystitis (n = 1), fever (n = 1) Laboratory toxicities Bilirubin increase (n = 10), ALP increase (n = 6), albumin increase (n = 6), lymphocyte count reduction (n = 6)
Cho (2016) (24)	32	13 (40.6)	Nausea/vomiting (n = 7), abdominal pain (n = 6)	1 (3.1)	Splenic infarction (n = 1)
Edeline (2016) (22)	34	-	-	6 (17.6)	Ascites (n = 5), pulmonary fibrosis (n = 1)
Pooled estimate (95% CI)		-		9 (3–27)	

Adverse events were defined and categorized in accordance with NCI-CTCAE version 5.0; meta-analytic pooled estimates were based on inverse variance method for calculating weights with random-effects model. ALP = alkaline phosphatase, GERD = gastroesophageal reflux disease, NCI-CTCAE = National Cancer Institute-Common Terminology Criteria for Adverse Events

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Table 4. Summary of Adverse Events Associated with SOR Treatment

First Author (Year)	No. of Patients	Grade 1/2 Toxicity Incidence (%)	Grade 1/2 Toxicity	Grade 3/4 Toxicity Incidence (%)	Grade 3/4 Toxicity
Jeong (2013) (8)	30	22 (73.3)	Fatigue (n = 10), HFS (n = 8), anorexia (n = 6), diarrhea (n = 6), rash/desquamation (n = 3), nausea (n = 2), bleeding (n = 1)	5 (16.7)	Fatigue (n = 3), HFS (n = 1), liver dysfunction (n = 1)
Nakazawa (2014) (31)	28	-	-	19 (67.9)	AST/ALT increase (n = 6), anorexia/nausea (n = 4), HFS (n = 3), ascites (n = 1), hepatic failure (n = 1), hypertension (n = 1), proteinuria (n = 1), sepsis (n = 1), thrombocytopenia (n = 1)
Song (2015) (10)	60	31 (52.3)	HFS (n = 23), fatigue (n = 17), diarrhea (n = 15), rash (n = 12), alopecia (n = 4), hypertension (n = 2)	19 (31.7)	Diarrhea (n = 8), fatigue (n = 5), HFS (n = 4), rash (n = 2)
Zhang (2015) (11)	44	-	HFS (n = 23), alopecia (n = 22), diarrhea (n = 16), weight loss (n = 15), fatigue (n = 12), hypertension (n = 2)	11 (25.0)	Diarrhea (n = 3), HFS (n = 3)*
Cho (2016) (24)	31	5 (16.1)	Diarrhea (n = 2), anorexia (n = 1), fever (n = 1), nausea/vomiting (n = 1)	5 (16.1)	Diarrhea (n = 2), abdominal pain (n = 1), bleeding (n = 1), nausea/vomiting (n = 1)
Edeline (2016) (22)	117	-	-	52 (44.4)	-
Ye (2017) (32)	110	52 (47.3)	-	6 (5.5)	-
Choi (2018) (34)	29	12 (41.4)	Hyperbilirubinemia (n = 7), HFS (n = 4), AST/ALT increase (n = 6), diarrhea (n = 4), alopecia (n = 3), ascites (n = 2), fever (n = 2), anorexia (n = 1)	15 (51.7)	AST/ALT increase (n = 5), HFS (n = 5), hyperbilirubinemia (n = 3), ascites (n = 2), diarrhea (n = 1)
Yoon (2018) (13)	44	29 (65.9)	HFS (n = 23), diarrhea (n = 16), nausea (n = 14), abdominal pain (n = 13), hypertension (n = 10), rash (n = 8), anorexia (n = 7), hoarseness (n = 6), fatigue (n = 5), mucositis (n = 4), bilirubin increase (n = 1)	12 (27.3)	Hypertension (n = 4), AST/ALT increase (n = 3), diarrhea (n = 2), HFS (n = 2), abdominal pain (n = 1), anorexia (n = 1), mucositis (n = 1)
Pooled estimate (95% CI)		49 (34–64)		28 (17–43)	

*Details of adverse events were incomplete in study. Adverse events were defined and categorized in accordance with NCI-CTCAE version 5.0; meta-analytic pooled estimates were based on inverse variance method for calculating weights with random-effects model. ALT = alanine aminotransferase, AST = aspartate aminotransferase, HFS = hand-foot syndrome

respectively), a high degree of study heterogeneity was noted in both.

When comparing the two treatment arms, radioembolization showed a lower rate of grade 3/4 AEs than sorafenib, but without statistical significance (9% vs. 28%; $p = 0.129$).

DISCUSSION

This meta-analysis showed that radioembolization may be an effective therapeutic option for the treatment of patients with HCC and PVTT, showing higher OS and longer TTP versus sorafenib. In addition, radioembolization was

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associated with a lower incidence of grade 3/4 AEs versus sorafenib.

The observed improvement in treatment outcomes associated with radioembolization could be explained by the fact that the main cause of death in patients with advanced HCC is intrahepatic progression, rather than the complications related to metastasis (24). One prospective study (35) showed that among 61 patients with HCC and PVTT who experienced cancer progression, 64% had intrahepatic progression while only 24% experienced extrahepatic metastasis prior to death. This indicates that a locoregional treatment, rather than systemic therapy, may play an important role in the management of HCC with PVTT. Indeed, responses to sorafenib therapy were seen to be poor in two studies, the Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol (36) and the Asia-Pacific trial (15), which demonstrated no complete responses and only 0.7–3.3% partial response. Therefore, TACE has been widely performed in patients with HCC and macrovascular invasion in Asian countries (37, 38). Radioembolization is an alternative locoregional treatment that induces tumor necrosis by delivering localized radiation via intra-arterial injection of ^{90}Y, thereby targeting the tumor with minimal risk of liver ischemia (39). The use of radioembolization can be supported by the results of two retrospective studies comparing radioembolization and sorafenib in patients with HCC and PVTT, with a higher OS observed in those undergoing radioembolization (22, 23). Although the "SorAfenib versus Radioembolization in Advanced Hepatocellular carcinoma" (SARAH) (14) and "Selective Internal Radiation Therapy Versus Sorafenib" (SIRveNIB) trials (40) failed to demonstrate the superiority of radioembolization versus sorafenib in terms of OS, these two studies were not restricted to HCC patients with PVTT. Therefore, although the results are still exploratory, radioembolization has considerable promise as a valuable therapeutic option for patients with HCC and PVTT.

In the present meta-regression analysis, a higher proportion of patients with ECOG 0, Child-Pugh class A, a previous history of HCC treatment, and a lower proportion of extrahepatic metastasis in the radioembolization group was associated with higher 1-year OS. In other words, patients with a better general condition and liver function without extrahepatic metastasis, or those who had previously undergone HCC treatment, may show better outcomes following radioembolization. Regarding extrahepatic metastasis, in the SARAH trial, patients undergoing radioembolization showed a significantly lower cumulative incidence of intrahepatic progression and significantly higher cumulative incidence of extrahepatic progression than those treated with sorafenib (14). This indicates the better local efficacy related to radioembolization. Therefore, radioembolization can be expected to be associated with improved efficacy in patients with HCC and PVTT confined to the liver. Considering these results, patients in a good general condition, with preserved liver function and no extrahepatic metastasis, may be considered to be good candidates for radioembolization. Further investigations using individual patient data are required for more detailed analyses of the indications for radioembolization.

In this meta-analysis, radioembolization showed a trend towards a lower incidence rate of grade 3/4 AEs than sorafenib (9% vs. 28%; $p = 0.129$). Although comparison of the incidence rates of grade 1/2 AEs was limited, the rate reported in one study using radioembolization (24) was slightly lower than the pooled incidence rate of sorafenib (40.6% vs. 49%; 95% CI, 34–64%). This suggests a better safety profile for radioembolization than sorafenib, which is in agreement with previous reports (14, 22, 24, 40). Two randomized controlled trials (SARAH and SIRveNIB) both demonstrated a lower incidence of any grade AEs with radioembolization versus sorafenib (77% vs. 93% and 60% vs. 85%, respectively); similar results were seen with respect to grade 3/4 AEs (41% vs. 63% and 28% vs. 51%, respectively). In addition, better quality of life was seen in the radioembolization group versus the sorafenib group (14, 40). In the SARAH trial, the rate of discontinuation of sorafenib due to drug-related toxicity reached 64%, and 78% of these patients discontinued the drug permanently. Two retrospective studies of populations restricted to HCC with PVTT also demonstrated a lower incidence of severe AEs in patients undergoing radioembolization versus sorafenib (3–18% vs. 16–45%) (22, 24). The safety profile associated with radioembolization is likely to result from its unique mode of action. Compared with TACE, it can produce anti-tumor effects without arterial obstruction, thereby minimizing the risk of liver ischemia regardless of PVTT. Moreover, the average depth of penetration of local radiation emitted from ^{90}Y is only 2.5 mm, which means that the adjacent liver parenchyma is spared from damage (39). However, it should be noted that radioembolization can cause several radiation-induced complications in the liver, gallbladder, and lungs (16). Therefore, while radioembolization may be associated with a better safety

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profile than sorafenib, comprehensive pretreatment evaluation should be conducted to reduce the risk of radiation-induced complications.

The current analysis has several limitations. First, the majority of the eligible studies (11 of 17, 65%) were retrospective, therefore introducing the risk of selection bias. Secondly, there were limitations in extracting the exact survival data from the study regarding censored subjects and how these might affect the results. Thirdly, only two studies were used for calculating pooled estimates of TTP in the radioembolization group, thereby reducing the robustness of the results. Further investigations seem mandatory to verify our results. Finally, substantial heterogeneity was observed regarding OS and TTP. Although this could affect the meta-analysis, the reasons for the study heterogeneity were explored thoroughly using meta-regression analysis.

In conclusion, radioembolization is an effective therapeutic option with a good safety profile that may be preferable to sorafenib in the treatment of HCC and PVTT. Patients in good general condition, with preserved liver function and no extrahepatic metastasis, may be good candidates for radioembolization. Further investigation will be required to clarify the best therapeutic strategy for patients with HCC and PVTT.

Supplementary Materials

The online-only Data Supplement is available with this article at https://doi.org/10.3348/kjr.2018.0496.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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