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Meta-Analysis

Efficacy of combined transarterial radioembolization and sorafenib in the treatment of hepatocarcinoma: A meta-analysis

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ABSTRACT

Background: Adjuvant sorafenib may further enhance the efficacy of transarterial radioembolization for the treatment of hepatocellular carcinoma.

Aims: To evaluate the efficacy and safety of radioembolization plus sorafenib in hepatocellular carcinoma patients.

Methods: With a literature search through October 2020, we identified 9 studies (632 patients). Primary outcome was overall survival. Results were expressed as pooled median, odds ratio, or hazard ratio and 95% confidence intervals.

Results: Pooled overall survival after radioembolization plus sorafenib was 10.79 months (95% confidence interval 9.19–12.39) and it was longer in Barcelona Clinic Liver Cancer (BCLC) B (14.47 months, 9.07–19.86) as compared to BCLC C patients (10.22 months, 7.53–12.9). No difference between combined therapy versus radioembolization alone was observed in terms of overall survival (hazard ratio 1.07, 0.89–1.30). Pooled median progression-free survival was 6.32 months (5.68–6.98), with 1-year progression-free survival pooled rate of 38.5% (12.7%-44.2%). No difference in progression-free survival (hazard ratio 0.94, 0.79–1.12) between the two treatments was observed. Pooled rate of severe adverse events was 48.9% (26.7%-71.2%), again with no difference between the two treatment regimens (odds ratio 1.52, 0.15–15.02).

Conclusions: The association of sorafenib does not seem to prolong survival nor delay disease progression in patients treated with radioembolization.

1. Introduction

Hepatocellular carcinoma (HCC) represents a major health issue, being the third most common cause of cancer-related death and the leading cause of mortality in cirrhotic patients.[1,2] Improvements in surveillance/screening protocols in addition to refined diagnostic tools have led to a consistent improvement in the early diagnosis of HCC, which is feasible in 30–60% of cases in developed countries.[3] Nevertheless, a considerable proportion of patients still develop extrahepatic metastases and/or tumoral portal vein thrombosis (PVT),[4] thus falling in an advanced stage of disease not suitable for curative treatments.

It is well known that patients with HCC and PVT are not amenable to transarterial chemoembolization (TACE), due to the high risk of ischemia and liver failure related to the impaired vascularization of the liver and compromised portal circulation.[2,5,6]

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Two pivotal phase III trials [7,8] have demonstrated a survival advantage for patients with advanced HCC treated with the oral multi-tyrosine kinase inhibitor sorafenib (Nexavar®, Bayer, Leverkusen, Germany). A survival advantage has been confirmed in the analysis of the subgroup of patients with PVT.[9] Therefore, sorafenib was approved as the standard of care for the treatment of advanced HCC worldwide.[2,10]

Yttrium-90 transarterial radioembolization (TARE) represents a form of liver-directed brachytherapy which has garnered an increasing role in the management of unresectable HCC in the last decade due to its efficacy by inducing necrosis and delaying tumor progression.[11–15] Among other advantages, TARE is a microembolic procedure that does not significantly alter the hepatic arterial flow, hence, it allows to overcome the major contraindication to TACE, namely PVT presence. In particular, in this subset of patients, TARE was found to provide competitive if not more favorable results as compared to sorafenib.[16,17]

However, despite these undoubted advantages, a non-negligible proportion of advanced HCC patients still do not benefit from TARE, thus calling for more effective therapeutic regimens.

It is well known that ischemia induced by intrahepatic locoregional therapies result in a local and systemic upregulation of vascular endothelial growth factor (VEGF) which can increase tumor angiogenesis.[6] VEGF represents one of the main therapeutical targets of the multikinase inhibitor sorafenib; therefore, a strong rationale support combining sorafenib and transarterial therapies in order to counteract the effects of VEGF.

Studies testing the combination of TACE and sorafenib have shown conflicting results, with the pivotal SPACE trial not reporting a clear benefit in terms of time-to-progression (TTP) but only a slight superiority in terms of time-to-unTACEable progression.[18]

On the other hand, evidence is still limited on the combination of TARE and sorafenib. This is of particular interest, as it has been reported that more than 50% of patients progressing after TARE are not eligible to sorafenib because of poor liver function.[19] Hence, it could be meaningful to start the therapeutic regimen with a combined approach aimed at treating patients effectively while amenable to treatment (i.e. with good liver function) rather than at tumor progression.

The recent multicenter SORAMIC trial failed to find a significant superiority of the combined regimen of TARE plus sorafenib versus sorafenib alone although subgroup analyses indicated a survival benefit in patients without cirrhosis, cirrhosis of non-alcoholic etiology, or patients ≤65 years old.[20]

Given the recent publication of single cohort studies and comparative series testing TARE plus sorafenib, we decided to perform a meta-analysis to evaluate the efficacy and the safety profile of combined therapy for the management of unresectable HCC.

2. Materials and methods

2.1. Selection criteria

The literature search strategy was based on the following inclusion criteria: (1) prospective or retrospective observational or cohort studies assessing TARE plus sorafenib alone or in comparison to other therapies in adult patients with unresectable HCC; (2) studies published in English; (3) articles reporting at least one of the following outcomes, namely overall survival (OS), progression-free survival (PFS), or adverse events (AE). Small case series <10 patients, review articles, and animal models were excluded.

2.2. Search strategy

Literature search was conducted on PubMed, EMBASE, Cochrane Library, and Google Scholar including all studies fulfilling the inclusion criteria published from inception to October 2020, based on the string (((radioembolization) AND (sorafenib)) AND (hepatocellular carcinoma[MeSH Terms])) OR (HCC[MeSH Terms]).

Relevant reviews in the field were examined for potential additional suitable studies. Authors of included studies were contacted to obtain full text or further information when needed. Manual search on the proceedings of the main international hepatological and gastroenterological conferences was also performed.

Data extraction was performed by 2 authors (AF and CC) and the quality of included studies was rated by 2 reviewers independently (AF and BPM) based on the Newcastle-Ottawa scale for non-randomized studies [21] or the Cochrane tool for assessing the risk of bias in the case of randomized-controlled trials (RCTs).[22] Disagreements were solved by discussion and after a third opinion (RS).

2.3. Outcomes assessed

The primary outcome was overall survival, defined as the time elapsed from the treatment to death or censoring. Secondary outcomes were survival rate at 1 and 2 years, progression-free survival (PFS, defined as time elapsed from treatment to radiological evidence of progression), PFS rate at 1 year, tumor response, both in terms of objective response (OR, defined as complete response + partial response) and disease control rate (DCR, defined as complete response + partial response + stable disease), and severe adverse event (SAE) rate.

As a secondary analysis, we compared OS and PFS of TARE plus sorafenib to TARE alone based on head-to-head comparative series.

2.4. Statistical analysis

Study outcomes were pooled through a random-effects model based on DerSimonian and Laird test, and results were expressed as rates and 95% confidence interval (CI). Comparison between TARE plus sorafenib and TARE alone was based on a random-effects model and results were expressed as odds ratio (OR) or hazard ratio (HR) and 95% CI, when appropriate.

The presence of heterogeneity was calculated through Cochran's Q test based on a chi-square distribution, which is computed as the weighted sum of squared differences between individual study effects and the pooled effect across studies, with the weights being those used in the pooling method.

Any potential publication bias was verified through visual assessment of funnel plots. Subgroup and sensitivity analysis was conducted based on tumor stage (Barcelona Clinic Liver Cancer [BCLC] B versus BCLC C), study design (prospective/RCT versus retrospective), microspheres used (resin versus glass), and start of sorafenib therapy (before versus after TARE).

In order to explore the impact of sorafenib dose and treatment duration on the primary endpoint, a meta-regression model was built based on a stepwise backward approach.[23]

All statistical analyses were conducted using RevMan (version 5.0 for Windows; the Cochrane Collaboration, Oxford, UK), OpenMeta[Analyst] software, and R 3.0.2 (R Foundation for Statistical Computing, Vienna, Austria), *metafor* package.[24]

For all calculations a 2-tailed P value of less than 0.05 was considered statistically significant.

3. Results

3.1. Studies

As shown in Fig. 1, of 106 studies initially identified, after screening out articles not fulfilling the inclusion criteria, 19 studies

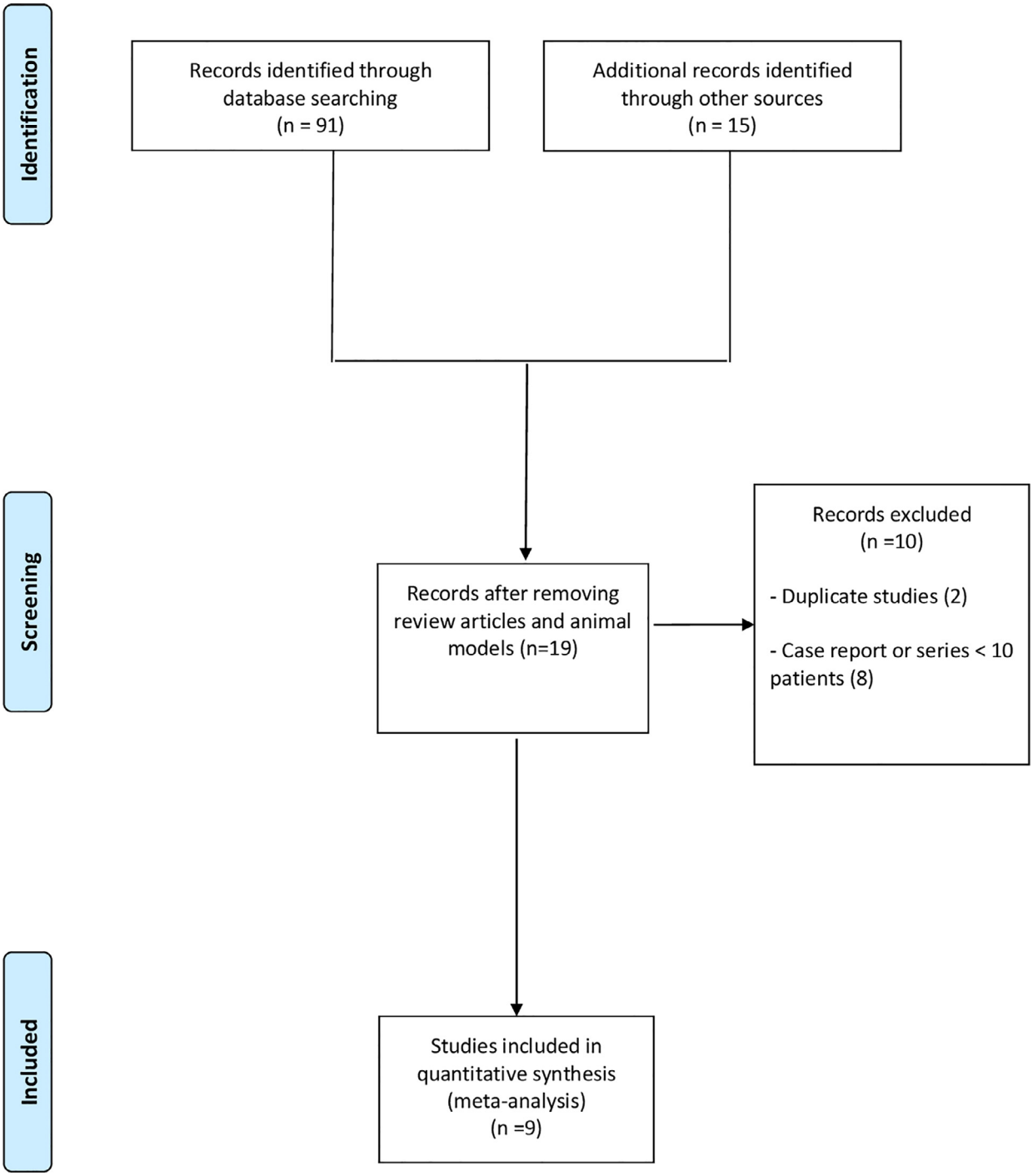

Fig. 1. Flowchart of the included studies.

were identified. After further exclusion of 8 small series <10 patients and 2 duplicate studies, [25,26] 9 articles with 632 patients were finally included in the meta-analysis.[20,27–34]

Of 9 included studies, 2 were RCTs (the aforementioned SORAMIC trial which compared TARE plus sorafenib versus sorafenib alone, of which only the arm treated with the combined therapy was included in the meta-analysis [20] and a small RCT comparing TARE plus sorafenib versus TARE alone in the pre-transplant setting [30]), 3 were retrospective case control studies comparing TARE plus sorafenib versus TARE alone, [28,29,34] 4 were non-comparative single cohort studies, of which 2 prospective [27,33] and 2 retrospective series.[31,32]

The main characteristics of the included studies were reported in Table 1. The recruitment period ranged from 2008 to 2018. All the studies except the series by Chow *et* al. [27] were published in Europe/America and the 5 comparative studies presented two well-balanced cohorts in terms of baseline patients characteristics. A single study was published as conference abstract,[28] but being published by an author of our group we had full access to the original dataset for adjunctive data not reported in the abstract.

TARE was performed using resin microspheres in 5 studies,[20,27,29,31,32] glass microspheres in 3 studies,[28,30,34] whereas in the study by Salman et al. the type of microspheres used was not specified.[33]

Table 1
Characteristics of included studies.

Study	Country	Sample size; Treatment	Study period/design	Control group (sample size)	Ageyears	Gender male	Child Pugh score/ Etiology viral	BCLC	Prior treatments/ Performance Status 0	AFP/Bilobar/ Extrahepatic spread	Activity delivered/Tumor response criteria	Start of sorafenib therapy/sorafenib treatment duration/dose (mg)
Chow 2014 [27]	Multicenter Asia	29; TARE with resin microspheres+ sorafenib	2008–2009/ Prospective	No	64.6 ± 10.6	21 (72%)	A: 20 (69%)/B: 9 (31%) NR	B: 11 (37.9%)/ C: 18 (62.1%)	7 (24%) 22 (76%)	NR/NR/11 (38%)	3 ± 1 GBq/RECIST	14 days after TARE/4.1 months±4.8/600±319.7
Facciorusso 2013 [28][a]	Italy	15; TARE with glass microspheres + sorafenib	2010–2012/ Retrospective	30; TARE with glass microspheres	NR	NR	A: 100%	B: 20% C: 100%	NR	NR/NR/0%	NR/ RECIST and EASL	2 months before TARE/9 months/600
Facciorusso 2020 [29]	Italy	45; TARE with resin microspheres + sorafenib	2011–2018/ Retrospective propensity score-matched	90; TARE with resin microspheres	62 (24–74) 62 (32–84)	33 (73.3%) 72 (80%)	A: 100% 33 (73.4%) A: 88 (97.7%)/B: 2 (2.3%) 60 (67%)	B: 9 (20%)/C: 36 (80%) B: 18 (20%)/C: 72 (80%)	33 (73.3%) 72 (80%)	40.8 (5–169,190)26.7%/0 48.2 (5–108,800)/20%/0	1.25 (0.35–4) GBq/RECIST and mRECIST	2 months before TARE/9 months/800 (200–800)
Kulik 2014 [30]	USA	10; TARE with glass microspheres + sorafenib	2009–2012/ RCT in pre-OLT setting	10; TARE with glass microspheres	58 (53–63) 60 (54–67)	8 (80%) 5 (50%)	A: 8 (80%)/B: 2 (20%) 8 (80%) A: 6 (60%)/B: 4 (40%) 6 (60%)	A: 7 (70%)/B: 1 (10%)/C: 2 (20%) A: 5 (50%)/B: 1 (10%)/ C: 4 (40%)	NR 8 (80%) NR 6 (60%)	14 (4.5–63.2) 2 (20%) 0 13 (1.5–484.6) 0 0	0.84 (0.41–1.82) GBq mRECIST 0.68 (0.35–1.31)	14 days before TARE/121 days (6–336)/489 (411–800)
Mahvash 2016 [31]	USA	19; TARE with resin microspheres + sorafenib	2008–2010/ Retrospective	No	67 (51–82)	14 (74%)	A: 16 (84%)/B: 3 (16%) 7 (37%)	B: 6 (32%)/ C: 13 (68%)	NR 6 (32%)	>400: 6 (32%)/NR/ 7 (37%)	41.2 (29.6–65.2) mCI/ RECIST and EASL	Median 58 days before TARE/224 days (49–732)/9 pts full dose
Rana 2013 [32]	USA	10; TARE with resin microspheres + sorafenib	2009–2012/ Retrospective	No	63.5 (56–76)	8 (80%)	A: 7 (70%)/B: 3 (30%) NR	C: 10 (100%)	4 (40%) NR	>400: 3 (30%)/NR/ 6 (60%)	27.8 (10.6–50.6) mCI/ RECIST	Median 43 days before TARE/NR/from 200 to 400
Salman 2016 [33]	Canada	29; TARE + sorafenib	2009–2012/ Prospective	No	63±12.5	26 (89.7%)	A. 23 (79.3%)/B: 6 (20.7%) 15 (51.7%)	A: 5 (17.2%)/B: 9 (31%)/ C: 15 (51.7%)	4 (13.7%)/ 11 (37.9%)	310 (24–957.8)/6 (20.7%)/8 (27.5%)	NR/ mRECIST	6 to 8 weeks before TARE/NR/NR
SORAMIC 2019 [20*]	Multicenter Europe	216; TARE with resin micro-spheres + sorafenib	2011–2016/ RCT	208; Sorafenib	66±13 66±13	181 (85.4%) 177 (85.5%)	A: 190 (90%)/ NR A: 190 (90%)	A: 6 (2.8%)/B: 62 (29.4%)/C: 143 (67.8%) A: 3 (1.5%)/B: 62 (30.1%)/C: 141 (68.4%)	51.4% NR 56.9% NR	NR/96 (56.8%)/52 (24.6%) NR/99 (56.6%)/46(22.2%)	1.7 ± 0.7/ NR	3 days after TARE/206±273/474.4 ± 335
Teyateeti 2020 [34]	USA	74; TARE with glass microspheres + sorafenib	2010–2018/ Retrospective	55; TARE with glass microspheres	63 (27–84) 70 (29–84)	58 (78.4%) 42 (76.4%)	A: 71 (95.9%)/B: 3(4.1%) 33 (44.6%) A: 50 (90.9%)/B: 5 (9.1%) 25 (45.5%)	B: 16 (21.6%)/C: 58 (78.4%) A: 5 (9.1%)/B: 22 (40%)/C: 27 (49.1%)/D: 1 (1.8%)	30 (40.5%)/38 (51.4%) 25 (46.4%)/27 (49.1%)	102.9 (1.5–656,373)/54 (73%)/19 (25.7%) 18.2 (1.9–109,307.7)/23 (41.8%)/0	3 (0.6–8.1) GBq RECIST 1.9 (0.5–5.8) GBq RECIST	Concurrently or within 1 month/NR/NR

Data are reported as absolute numbers (percentages) or mean (± standard deviation or with range).
Abbreviations: AFP, Alpha-FetoProtein; BCLC, Barcelona Clinic Liver Cancer; NR, Not Reported; TARE, Trans-Arterial Radio-Embolization.
[a] Study published as conference abstract.
* Only patients in the combined treatment arm were included in the meta-analysis.

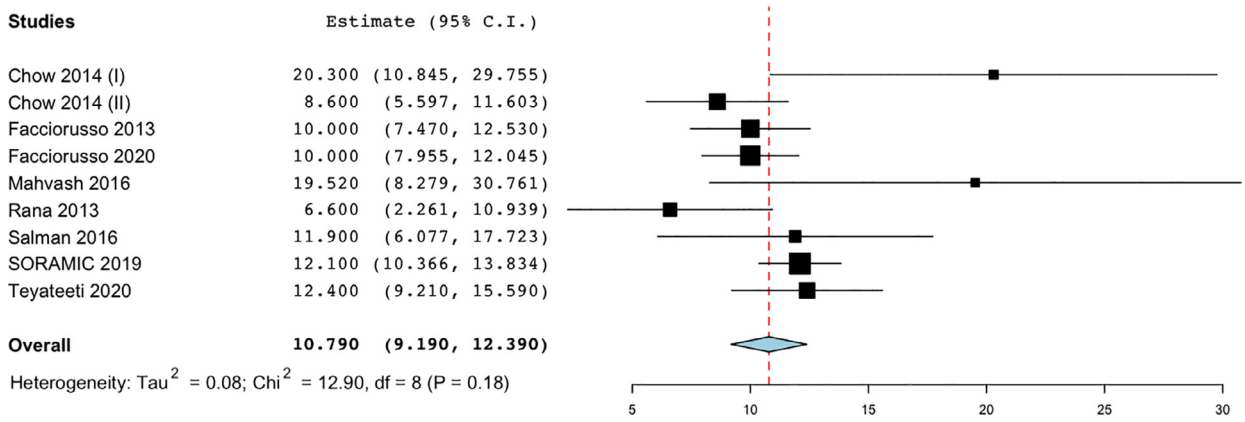

Fig. 2. Forest plot of pooled median overall survival.
Pooled overall survival after transarterial radioembolization+sorafenib was 10.79 months (95% CI 9.19–12.39) with no evidence of significant heterogeneity ($Chi^2 = 12.90$, $df = 8$, $p = 0.18$).
The size of the squares in the Forest plot is proportional to the weight of each study, which indicates its relative impact on the calculations of the common effect.

Table 2
Subgroup and sensitivity analysis of overall survival. Subgroup analysis was performed based on tumor stage (BCLC B versus BCLC C); sensitivity analysis was performed based on a) study design (prospective/RCT versus retrospective), b) microspheres used (resin versus glass), c) start of sorafenib therapy (before versus after radioembolization).

Variable	Subgroup	No. of Cohorts	No. of patients	Median survival (95% CI)	Within-group heterogeneity (Chi[2])
Overall survival					
Tumor stage	**BCLC B**	4	42	14.47 (9.07–19.86)	10.5 ($p = 0.31$)
	BCLC C	4	125	10.22 (7.53–12.9)	11.3 ($p = 0.44$)
Study design	**Prospective**	4	274	11.61 (8.58–14.65)	10.8 ($p = 0.38$)
	Retrospective	5	163	10.3 (8.29–12.31)	12.6 ($p = 0.20$)
Microspheres	**Resin**	6	319	10.69 (8.25–13.12)	10.9 ($p = 0.40$)
	Glass	3	118	11.02 (9.15–12.9)	7.8 ($p = 0.65$)
Sorafenib start	**Before TARE**	5	118	9.92 (8.01–11.82)	12 ($p = 0.23$)
	After TARE	4	319	11.72 (9.11–14.32)	12.8 ($p = 0.19$)

Abbreviation: BCLC, Barcelona Clinic Liver Cancer; CI, Confidence Interval; TARE, Trans-Arterial RadioEmbolization.

The majority of patients were in Child Pugh (CP) A and BCLC C stage, whereas Eastern Cooperative Oncology Group (ECOG) performance status 0 was predominant. Only a limited number of patients presented extrahepatic spread and in 4 series the tumoral disease was limited to the liver in all subjects.[28–30,34]

Mean activity delivered through TARE ranged from 0.8 to 3 GBq and tumor response was assessed mainly according to RECIST criteria,[35] while modified RECIST (mRECIST) [36] was used in 3 studies.[29,30,33]

Quality was deemed mainly moderate to high, with 3 studies rated as low quality.[28,32,34]

Details on the quality assessment of the included articles are shown in Supplementary Table 1.

3.2. Overall survival

As depicted in Fig. 2, pooled overall survival after TARE plus sorafenib was 10.79 months (95% CI 9.19–12.39) with no evidence of significant heterogeneity (Chi^2=12.90, $p = 0.18$). As expected, median OS was longer in BCLC B stage (14.47 months, 9.07–19.86) as compared to BCLC C subjects (10.22 months, 7.53–12.9; Table 2).

Table 2 reports the findings of sensitivity analysis conducted according to a) study design (prospective/RCT versus retrospective), b) microspheres used (resin versus glass), and c) sorafenib treatment regimen (before versus after TARE). Sensitivity analysis confirmed the results of the main analysis, with no evidence of significant heterogeneity.

Meta-regression aiming to correlate mean sorafenib dose and treatment duration with the primary outcome did not find any significant impact of these variables on overall survival (Supplementary Figures 1 and 2).

As reported in Table 3, pooled survival rates at 1- and 2-year were 51% (42.7%–59.3%) and 24.4% (19.7%–29.1%), respectively.

Supplementary Figure 3 reports the forest plot of the comparison between TARE plus sorafenib versus TARE alone in terms of overall survival. Based on 3 studies,[28,29,34] no difference in terms of overall survival (HR 1.07, 0.89–1.30) nor of 1-year survival rate (OR 0.78, 0.49–1.25) was observed, with no evidence of heterogeneity.

3.3. Secondary outcomes

Secondary efficacy outcomes were reported in Table 3.

3.3.1. Progression-free survival

As reported in Fig. 3, pooled median progression-free survival was 6.32 months (5.68–6.98), with 1-year PFS pooled rate of 38.5% (12.7%–44.2%). As reported in Supplementary Figure 4, no difference in terms of PFS (HR 0.94, 0.79–1.12) nor of 1-year PFS rate (OR 1.31, 0.66–2.61) between TARE plus sorafenib versus TARE alone was observed, with no evidence of heterogeneity.

3.3.2. Tumor response

Pooled rates of objective response and disease control rate were 27% (18.2%–35.8%) and 80.1% (65.1%–95.2%), respectively. Heterogeneity in objective response analysis was not significant (Chi^2=4.53, degrees of freedom [df]=6, $p = 0.15$) whereas high evidence of heterogeneity (Chi^2=19.34, df=5, $p = 0.03$) was observed in disease control rate analysis. Subgroup analysis based on the response criteria (RECIST vs mRECIST vs EASL) was not feasible due to the limited number of studies, hence these results should be interpreted with caution.

Table 3
Other outcomes analyzed and results of comparative analysis with transarterial radioembolization alone.

Outcome	Subgroup	No. of Cohorts	No. of patients	Summary Estimate (95% CI)	Within-group heterogeneity (Chi[2])
Survival rate	**1-year survival rate**	6	382	51% (42.7%–59.3%)	2.23 ($p = 0.20$)
	2-year survival rate	5	338	24.4% (19.7%–29.1%)	2.12 ($p = 0.21$)
Progression-free survival	**Overall**	7	192	6.32 (5.68–6.98)	1.23 ($p = 0.48$)
	1-year PFS rate	5	103	38.5% (12.7%–44.2%)	3.48 ($p = 0.18$)
Tumor response	**Objective response**	7	147	27% (18.2%–35.8%)	4.53 ($p = 0.15$)
	Disease control	6	132	80.1% (65.1%–95.2%)	19.34 ($p = 0.03$) I^2=58%
Severe adverse events	**Overall**	7	422	48.9% (26.7%–71.2%)	8.56 ($p = 0.13$)
Comparative analysis					
Survival rate	**Overall survival**[a]	3	134	1.07 (0.89–1.30)	1.06 ($p = 0.59$)
	1-year survival rate[b]	3	309	0.78 (0.49–1.25)	1.52 ($p = 0.43$)
Progression-free survival	**Overall**[a]	3	134	0.94 (0.79–1.12)	1.47 ($p = 0.48$)
	1-year PFS rate[b]	3	200	1.31 (0.66–2.61)	1.43 ($p = 0.45$)
Severe adverse events	**SAE rate**[b]	2	264	1.52 (0.15–15.02)	13.45 ($p = 0.08$)

Abbreviation: CI, Confidence Interval; PFS, Progression-Free Survival; SAE, Severe Adverse Event.
[a] Results expressed in terms of hazard ratio.
[b] Results expressed in terms of odds ratio.

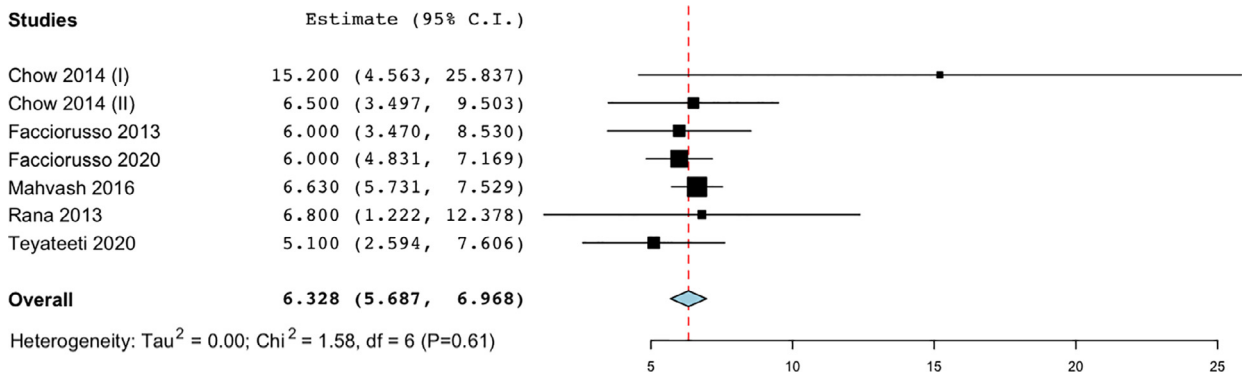

Fig. 3. Forest plot of pooled median progression-free survival
Pooled median progression-free survival after transarterial radioembolization+sorafenib was 6.32 months (95% CI 5.68–6.98) with no evidence of significant heterogeneity ($Chi^2 = 1.58$, df = 6, $p = 0.61$).
The size of the squares in the Forest plot is proportional to the weight of each study, which indicates its relative impact on the calculations of the common effect.

3.3.3. Severe adverse events

Pooled rate of SAEs was 48.9% (26.7%–71.2%), with no evidence of significant heterogeneity (Chi^2=8.56, df = 6, $p = 0.13$). Most frequent SAEs reported in the included studies were liver decompensation and sorafenib-related events, such as hand-foot syndrome, diarrhea and fatigue. The detailed list of severe adverse events was reported in the Supplementary Table 2.

Based on 2 studies,[29,34] no difference between the two treatment regimens concerning SAE rate was registered (OR 1.52, 0.15–15.02), again with no evidence of significant heterogeneity (Chi^2=13.45, df = 1, $p = 0.08$).

4. Discussion

In the last decades, a number of effective systemic therapies such as lenvatinib and atezolizumab and bevacizumab, have been tested and introduced in clinical practice for the management of unresectable HCC with promising results.[37,38] However, combining systemic agents with loco-regional treatments might represent a therapeutic tool in the armamentarium of hepato-oncology.

The combined treatment of sorafenib and TARE has a strong scientific rationale, as already pointed out with TACE.[39] In fact, locoregional treatments induce tumor ischemia, resulting in a consistent increase in VEGF and other hypoxia-induced factors. Concomitantly, the well-known antiangiogenetic activity of sorafenib acts by inhibiting specific receptors of such molecules.[39] Moreover, the antiangiogenetic effect of sorafenib could theoretically enhance the efficacy of TARE by reducing eventual artero-venous shunts as suggested by preliminary reports.[40]

In spite of the disappointing results of a large preliminary RCT,[20] other studies were published with the aim to evaluate the possible synergistic effects of sorafenib and TARE. Of note, the results of the aforementioned preliminary RCT - the phase II SORAMIC trial, should be interpreted with caution given the relevant proportion of randomized patients who were excluded due to major protocol deviations.[20] Furthermore, subgroup analyses of the SORAMIC trial found specific patient groups with potential clinical benefit from combined therapy, namely non-cirrhotic and younger subjects and patients presenting with HCC of non-alcoholic etiology.[20]

In attendance of the results from the ongoing STOP-HCC trial, conducted by a leading American group,[41] our meta-analysis represents the first attempt to provide a systematic overview of the efficacy and safety of the combined therapy TARE plus sorafenib, overall and in comparison to TARE alone.

Through a meta-analysis of 9 studies, we made several key observations. First, pooled overall survival after TARE plus sorafenib was 10.79 months (95% CI 9.19–12.39) and, as expected, it was longer in BCLC B stage (14.47 months, 9.07–19.86) as compared to BCLC C subjects (10.22 months, 7.53–12.9). These results are in line with the outcomes of TARE alone reported in the literature [12,13] and were confirmed in the comparative analysis based on RCTs/case-control studies (HR 1.07, 0.89–1.30). Therefore, our meta-analysis confirms the results of individual studies on the non-superiority of the combined approach over TARE alone in unre-

sectable HCC patients. Several reasons could help to explain this observation, in particular the high number of severe adverse events which can lead to sorafenib treatment discontinuation or dose escalation, thus limiting the efficacy of the oral chemotherapy. Moreover, most patients experiencing tumor progression after TARE plus sorafenib or sorafenib-related adverse events were not amenable to further systemic treatments, such as regorafenib,[42] and this aspect represents a further limitation to the therapeutic armamentarium in these patients.

Some technical aspects of the procedure, such as the kind of microspheres used (whether resin or glass), or the sorafenib treatment regimen adopted (starting chemotherapy before or immediately after TARE) did not result as significant predictors of overall survival, as reported in the sensitivity analyses.

Likewise, pooled PFS was 6.32 months (5.68–6.98), with no difference between TARE plus sorafenib versus TARE alone (HR 0.94, 0.79–1.12). Analysis of tumor response was weakened by the limited number of included studies and the heterogeneity of response criteria; however, a non-superiority of one therapeutic regimen over the other is expected based on survival analysis.

TARE is well-known to potentially lead to serious adverse events and the narrow safety profile limited its use worldwide in spite of favorable efficacy outcomes and cost-effective benefits.[43] As already reported in individual studies, pooled rates of SAEs was high (48.9%, 26.7%–71.2%) with the combined regimen, but not significantly higher than TARE alone (OR 1.52, 0.15–15.02).

As correctly noted in a recent meta-analysis,[44] the aforementioned high proportion of patients excluded from the trials testing TARE might lead to a discrepancy between per-protocol and intention-to-treat analysis. This may be mainly due to liver function deterioration/tumor progression between randomization and TARE treatment as well as technical contraindications to radioembolization (for example liver-to-lung shunting) not assessed before patient recruitment. These aspects should be properly taken into account in future trials which should accurately ascertain eligibility before randomization and early TARE delivery.

There are some limitations to our study. First, the low number of included studies and the merging of retrospective studies and RCTs call for a note of caution in the interpretation of our results. Second, progression-free survival could be an unreliable endpoint in HCC patients because death resulting from cirrhosis might confound detection of potential benefits from treatment. However, since included studies enrolled patients with well-preserved liver function, the impact of death unrelated to tumor progression was likely to be minimized. Third, the very limited number of comparative studies and RCTs prevented a valid assessment of the direct comparison between combined therapy and TARE alone. Finally, considerations of the economic impact of combined regimen were beyond the scope of this study. These limitations highlight the opportunity for future work in this field including well designed head-to-head trials to compare these two treatments.

In spite of these boundaries, our study represents the first meta-analysis assessing the efficacy and safety of combined TARE plus sorafenib, overall and in comparison to TARE alone, in the field of unresectable HCC. Our report could pave the way for future research into newer therapeutic schemes for advanced cancer patients. Results of the ongoing large randomized STOP-HCC trial (NCT01556490) are warranted in order to put in context the findings of the current manuscript. Furthermore, since the introduction of newer systemic treatments, a recent RCT showed interesting results on the combination of TARE plus Nivolumab [45] whereas an ongoing trial on TARE followed by atezolizumab and bevacizumab (NCT04541173) will likely pave the way to the further development of combined systemic and loco-regional treatments for the management of unresectable HCC.

5. Conclusion

The state of the science of loco-regional treatments combined with systemic drugs is an evolving field. Our meta-analysis shows that combined sorafenib plus TARE does not seem to modify outcomes nor safety profiles in advanced HCC patients, as compared to TARE alone. Further data of large randomized controlled studies are needed in order to confirm our findings and guide clinicians in navigating therapeutic algorithms for managing unresectable HCC.

Declaration of Competing Interest

None of the authors have any conflicts of interest to declare.

Author contributions

Study design: Antonio Facciorusso. Data collection: Antonio Facciorusso, Nicola Tartaglia, Rosa Paolillo, Daryl Ramai, Babu P Mohan, Christian Cotsoglou, Saurabh Chandan, Antonio Ambrosi, Irene Bargellini. Data analysis: Antonio Facciorusso. Draft writing: Antonio Facciorusso, Rodolfo Sacco, Matteo Renzulli. All the authors approved the final manuscript.

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Disclosures

The authors have no conflicts of interest to declare.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.dld.2021.06.003.

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